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APPENDICAL OXYURIASIS AND APPENDICITIS

BASED ON A STUDY OF 26,051 APPENDIXES

HAROLD GORDON, M.D.

ANN ARBOR, MICH.

In a study [1] of the incidence of oxyurids in 20,969 extirpated appendixes completed in 1930, attention was directed to the increasing frequency of appendical oxyuriasis. Since then, histologic examination of 5,082 additional appendixes, removed surgically, has revealed oxyurids in 90 instances, an incidence of 311 appendixes infested with pinworms in a total of 26,051 (1.19 per cent). In addition to oxyurids, amebas were found in 4 appendixes (1 the subject of report [2]), Taenia saginata in 1 and Ascaris lumbricoides in 3. There were no examples of infestation with Trichuris trichiura. In view of the increasing incidence of appendical oxyuriasis, its etiologic relationship to appendicitis becomes a matter of interest and importance.

REVIEW OF THE LITERATURE

While appendical helminthiasis had been described many years before, Still and Metchnikoff must be given chief credit for arousing interest in the condition. Still [3] found a high incidence of oxyuriasis in children at autopsy. He noted certain differences in the gross between the appendixes containing oxyurids and those showing acute inflammation. In the former type there were always injection of the serosa, thickening of the wall and chronic catarrh. Metchnikoff [4] directed attention to a possible relationship between appendicitis and intestinal parasitism, although he was concerned with trichuriasis rather than with infestation with oxyurids. Rheindorf [5] has been a staunch and vigorous proponent of the theory of a causal relationship between oxyuriasis and appendi-

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From the Department of Pathology, University of Michigan; C. V. Weller, Director.

1. Gordon, H.: Ann. Int. Med. **4**:1521, 1931.
2. Harrison, W. F.: Ann. Int. Med. **2**:1081, 1929.
3. Still, G. F.: Brit. M. J. **1**:898, 1899.
4. Metchnikoff, L.: J. d. praticiens **15**:185, 1901.
5. Rheindorf, A.: (*a*) Berl. klin. Wchnschr. **49**:451 and 503, 1912; (*b*) Med. Klin. **9**:53, 96, 133 and 177, 1913; (*c*) Frankfurt. Ztschr. f. Path. **14**:212, 1913; (*d*) Med. Klin. **9**:623, 1913; (*e*) Berl. klin. Wchnschr. **51**:1211 and 1271, 1914; (*f*) Centralbl. f. Bakt. **74**:604, 1914; (*g*) Die Wurmfortsatzentzündung, Berlin, S. Karger, 1920.

citis. His arguments, as well as the opposite views of Aschoff [6] and his pupils, Hueck [7] and Brauch,[8] are discussed in detail in a later section.

Hippius and Lewinson [9] believed that oxyurids are capable of causing traumatic injuries to the mucosa of the appendix, thus producing a favorable portal for the entrance and multiplication of pathogenic microorganisms. Wagener [10] concurred in this view. Riff,[11] favoring the thesis of a positive causal relationship, adduced the further arguments that oxyuriasis and appendicitis are most frequent between the ages of 5 and 20, that neither oxyuriasis nor appendicitis occurs before the twenty-first day of postnatal life, and that there is some evidence that appendicitis is a familial and a contagious disease. Fischer [12] used somewhat similar arguments to advance a negative view. He pointed out that appendicitis is relatively rare and oxyuriasis comparatively frequent before the tenth year. He stressed the finding of oxyurids in only 5 of 51 inflamed appendixes as against their presence in 29 of 105 and 32 of 39 normal appendixes. Finally, he drew attention to the reputed rarity of appendicitis in the native Chinese despite the extraordinary frequency of oxyuriasis among Orientals.

Drigalski and Koch [13] found the same percentage of oxyuriasis in 100 children from whom the appendixes had been removed and in 100 control subjects of similar age groups. Schröpl,[14] prompted by the observation of certain nervous manifestations in patients harboring oxyurids, tested the toxicity of the parasites by injecting an alcoholic extract of their bodies. He noted an increased reaction of sensitization of the skin, and he believed that the parasites are capable of provoking an immediate local, as well as a systemic, effect. Ragaine [15] and Garin [16] supported the view that intestinal parasites frequently may cause inflammation in the appendix. Garin emphasized especially the capacity of the oxyurids for inoculating the appendix with pathogenic microorganisms. MacLean [17] found enormous numbers of parasites in the appendixes of Chinese at autopsy, without any important sign of inflammation. He concluded that while oxyurids are capable of penetrating

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6. Aschoff, Ludwig: (*a*) Die Wurmfortsatzentzündung, Jena, Gustav Fischer, 1908; (*b*) Ergebn. d. inn. Med. u. Kinderh. **9**:1, 1912; (*c*) Med. Klin. **9**:249, 1913; (*d*) Berl. klin. Wchnschr. **51**:1504, 1914; (*e*) ibid. **57**:1041, 1920.
7. Hueck, O.: Frankfurt. Ztschr. f. Path. **13**:434, 1913.
8. Brauch, M.: Beitr. z. path. Anat. u. z. allg. Path. **71**:207, 1923.
9. Hippius, A., and Lewinson, J.: Deutsche med. Wchnschr. **33**:1780, 1907.
10. Wagener, O.: Virchows Arch. f. path. Anat. **182**:145, 1905.
11. Riff, A.: Presse méd. **27**:521, 1919.
12. Fischer, W.: Deutsche Ztschr. f. Chir. **183**:222, 1923.
13. Drigalski, W., and Koch, E. W.: Deutsche med. Wchnschr. **51**:309, 1925.
14. Schröpl, E.: Deutsche med. Wchnschr. **52**:1508, 1926.
15. Ragaine, Paul: L'appendicite vermineuse, Thèse de Paris, 1905, no. 85; quoted by Hueck.[7]
16. Garin, C.: Gaz. d. hôp. **83**:1455, 1910.
17. MacLean: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **21**:36, 1909.

beneath the mucosa, they cannot be considered seriously as factors in the causation of appendicitis.

Eastwood [18] examined both surgical and autopsy specimens and found pinworms in about the same proportion in each group. He found no evidence suggesting that the parasites are a frequent cause of appendicitis. Ney [19] distinguished three classes of infestation of the appendix with pinworms: a group showing worms, but without symptoms, common in children; a group grossly negative, but with microscopic inflammatory foci, and a group with gross and microscopic evidences of inflammation, which may progress to gangrene. His microscopic description, however, was neither detailed nor convincing. Harris and Browne [20] believed that the parasites are capable of provoking a morbid response because of the presence of degenerative and exudative changes about them with the destruction of tissue in their wake. However, they admitted that "those appendixes demonstrating positive worms in the gross could not be differentiated through the histopathologic study from those which were negative for the nematodes."

Innes and Campbell [21] found infestation with oxyurids much less frequently in normal than in inflamed appendixes. They supported the theory of a clinical type of appendicitis caused by oxyurids, but could find no relationship between suppurative appendicitis and infestation with nematodes. Cecil and Bulkley [22] grouped their material in four divisions:

1. Appendixes containing oxyurids as a coincidence. These showed only mild catarrh and lymphoid hyperplasia.
2. Appendixes showing penetration of the mucosa with punctate hemorrhages but without inflammatory reaction.
3. Appendixes in which oxyurids were present and producing destructive, ulcerous lesions in the mucosa.
4. Gangrenous appendixes showing occurrence of oxyurids; the relationship, however, is a matter of some uncertainty.

They stressed the presence of mild catarrh and lymphoid hyperplasia as almost constant accompaniments of oxyuriasis. To them, these changes constituted important signs of reaction, since they were present in a control group of appendixes obtained at autopsy and containing worms, as well as in those removed at operation. However, the very fact that they were present in the control group and likewise in many appendixes not containing worms argues that these changes can be provoked by causes other than parasites. Cecil and Bulkley explained the paucity of inflammatory changes on the basis of a negative chemotaxis, but also stressed the fact that it is practically impos-

18. Eastwood, E. H.: J. Path. & Bact. **26**:69, 1923.
19. Ney, G. C.: Bull. Johns Hopkins Hosp. **23**:123, 1912.
20. Harris, W. H., and Browne, D. C.: J. A. M. A. **84**:650, 1925.
21. Innes, J. A., and Campbell, A. E.: Parasitology **7**:189, 1914.
22. Cecil, R. L., and Bulkley, K.: J. Exper. Med. **15**:225, 1912.

sible to make complete serial sections of the appendix, so that very minute hemorrhages may be missed.

Suzuki [23] compared operative and postmortem appendixes, and noted hemorrhages in the former, but none in the latter group when the parasites occurred in the appendical wall. He related this difference to the motility of the parasites in the surgical specimens, and to their quiescence in the necropsy material. He proposed the term "appendicopathia oxyurica traumatica" for appendixes showing this change. Suzuki [23] classified the extirpated appendixes in three groups. The first two correspond essentially to the first two groups of Cecil and Bulkley,[22] except for the suggested nomenclature "appendicopathia oxyurica traumatica." A third group, of which he found but a single example, he termed "appendicitis oxyurica" because of an essential causal relationship between the parasites and the inflammation. Aschoff,[6c] Hueck [7] and Brauch [8] also believed that the worms are capable of provoking painful muscular spasms in the appendix.

Ssolowjew [24] found shallow half moon-shaped depressions in the mucosa accompanied by karyolysis, pressure atrophy and local eosinophilia. He believed that these changes favored secondary bacterial invasion, thus ascribing an indirect rôle to the parasites. Such a relationship, however, was not subject to histologic verification in every instance. Steichele [25] concluded that true appendicitis cannot be distinguished clinically from the painful syndrome evoked by the parasites. Jaroschka [26] expressed a similar view. He believed that the oxyurids are capable of causing local damage to the wall of the appendix, either by mechanical pressure or by toxic action, these changes being accompanied by pain. True appendicitis, however, occurred only rarely in association with the worms.

In addition to the more elaborate studies cited, the literature abounds with brief clinical reports. Nicolaus [27] reported five examples of appendical oxyuriasis. He found threadworms in the wall of the organ and offered evidence in support of the claim that the penetration had taken place as a preoperative, vital phenomenon. Ehlers [28] described an instance of appendicitis of acute onset. The appendix contained numerous pinworms and showed mucosal defects differing from those produced by "paraffin impregnation." He noted acute periappendicitis, and ascribed this to fecal absorption. Rheindorf [5b] drew attention to identical changes. Wood [29] reported a group of seven appendixes removed at operation, all containing oxyurids. He described symptoms differing clinically from those usually associated with appendicitis.

23. Suzuki, K.: Surg., Gynec. & Obst. **21**:702, 1915.
24. Ssolowjew, N. J.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **41**:20, 1928.
25. Steichele, H.: Arch. f. klin. Chir. **135**:373, 1925.
26. Jaroschka, K.: Deutsche Ztschr. f. Chir. **183**:99, 1923.
27. Nicolaus, H.: Deutsche Ztschr. f. Chir. **215**:133, 1929.
28. Ehlers, H. W. E.: Deutsche Ztschr. f. Chir. **213**:275 1929.
29. Wood, W. A.: M. J. Australia **1**:234, 1918.

Garlough [30] noted acute or subacute inflammatory changes, many polymorphonuclear leukocytes and from a few to many eosinophils in appendixes containing pinworms. Bloom [31] found pinworms of minor importance in his series. The individual case reports presented by Wakefield,[32] Culhane,[33] Rogers,[34] Lediard [35] and Ashhurst [36] offer data insufficient for a well considered opinion.

In summary, it may be said of the literature that much of it is only too evidently founded on conviction instead of on objective data. Some of the authors have been forced to bolster their theses by arguments based on analogy, and the conscientious reader is more apt to be confused than helped by the mass of evidence available.

MATERIAL AND METHODS

My material consisted of 26,051 appendixes received for routine diagnosis at the pathologic laboratories of the University of Michigan during the period from July 1, 1894, to Oct. 31, 1932. Only surgical specimens were included in this group. For reasons to appear later, autopsy specimens were not considered necessary for control purposes. Most of the appendixes came from residents of Michigan, and were removed in the University Hospital and in other hospitals distributed over the state.

The appendixes were received in 10 per cent formaldehyde. Since the beginning of 1903, blocks for impregnation with paraffin have been taken as a routine measure to include representative portions of the proximal, mesial and distal thirds, while prior to that period the organs were sectioned at but one or two levels. When indicated, blocks have been taken from four or more levels. Duplicate sections were usually prepared, but serial sections were not attempted since the technical procedure was purely routine. In the course of the present study many of the old blocks have been resectioned. With few exceptions, the diagnoses for the entire series have been rendered by the directors of the laboratories, Dr. A. S. Warthin and Dr. C. V. Weller.

In conducting this study, the following outline was followed:

1. Anatomic distribution of the parasites and the incidence of such distribution
2. Pathologic changes
   - (*A*) The lesions
     - (*a*) Incidence
     - (*b*) Description
     - (*c*) Incidence of catarrhal reaction
   - (*B*) Response of the lymphoid tissue
   - (*C*) Local eosinophilia
3. Clinical significance
4. Conclusions

30. Garlough, L. N.: J. A. M. A. **80**:422, 1923.
31. Bloom, C. J.: New Orleans M. & S. J. **81**:377, 1928.
32. Wakefield, R. W.: J. A. M. A. **50**:1904, 1908.
33. Culhane, T. H.: J. A. M. A. **54**:48, 1910.
34. Rogers, L.: New York M. J. **118**:620, 1923.
35. Lediard, H. A.: Edinburgh M. J. **32**:762, 1925.
36. Ashhurst, A. P. C.: Am. J. M. Sc. **138**:583, 1909.

RESULTS

ANATOMIC DISTRIBUTION OF THE PARASITES

In table 1 is shown the anatomic relationship of the parasites to the structure of the appendix. The parasites were present in the lumen alone in 256 instances (82.31 per cent). In 22 additional appendixes, however, while oxyurids were present in the lumen, they were more intimately related to the mucosa. In this group the mucosa showed shallow half moon-shaped depressions approximately corresponding in size and in shape to the worms. Of the remaining 33 appendixes, 17 had pinworms both in the submucosa and in the lymphoid follicles, 12 contained them in the submucosa alone, and 4, in the lymphoid follicles only.

TABLE 1.—*Anatomic Relationship of the Oxyurids to the Structure of the Appendix*

Location of Oxyurids	Cases	Percentage
In the lumen (not attached to mucosa)	256	82.31
In the lumen (attached to mucosa)	22	7.07
In the submucosa and in the lymphoid follicles	17	5.47
In the submucosa only	12	3.86
In the lymphoid follicles only	4	1.29
Total	311	

These figures are in general agreement with the findings of other investigators. Rheindorf [5a, b, c] has persistently reported a much higher incidence of penetration. This, he claimed, may not be apparent unless serial sections are prepared, and the entire appendix is sectioned.

PATHOLOGIC CHANGES IN APPENDICAL OXYURIASIS

The Lesions.—Incidence and Description: In 12 of the 22 appendixes containing oxyurids in intimate relationship to the mucosa, there were lesions peculiar to the parasites and unquestionably related to them. In 6 the lesions could not with certainty be ascribed to the worms, while in the remaining 4 no characteristic lesions could be demonstrated. The lesions ascribed to the worms varied in degree and in extent, so that an uninterrupted series could be built up from small half moon-shaped depressions to actual, although shallow, erosions (figs. 1 and 2). In some instances the defects represented simply the results of pressure. My material shows that pressure effects occur particularly when worms are caught between a fecal concretion and the mucosa. This relationship may escape recognition if the concretion has been dislodged in the sectioning of the appendix. When local defects corresponding to the position of the worms are associated with dilatation of the lumen and general atrophy of the mucosa, the effect of such calculi can be deduced. These lesions may show flattening of an epi-

thelium which is still smooth and intact, and are characterized only by a locally increased production of mucin. In a lesion of more marked degree there is an approach to true ulceration. These erosions have certain peculiarities by which they may be recognized. They are small

Fig. 1.—Small pressure lesion in the mucosa, showing the oxyurid responsible for the lesion. Note the fine membrane adherent to the parasite. Hemalum and eosin stain; × 100.

and lie in close relationship to the causal worms; minute punctate hemorrhages may be nearby, and along the free surface of each erosion may be seen a fine membrane composed of desquamated epithelial cells, mucin and lymphocytes. Part of the membrane may be adherent, also, to the worm (fig. 1).

In contrast to the lesions described, some appendixes contain mucosal defects without any evidence of tissue reaction or hemorrhage. A defect of the latter type is shown in figures 3, 4 and 5, which represent different levels cut from the same block of tissue. Such appendixes are smooth-walled, and there is no trace of hemorrhage or of an alterative, defensive or protective reaction. In the submucosa and the lymphoid tissue of the appendixes containing oxyurids are changes analogous to the second type of mucosal defects. In this group the worms lie in

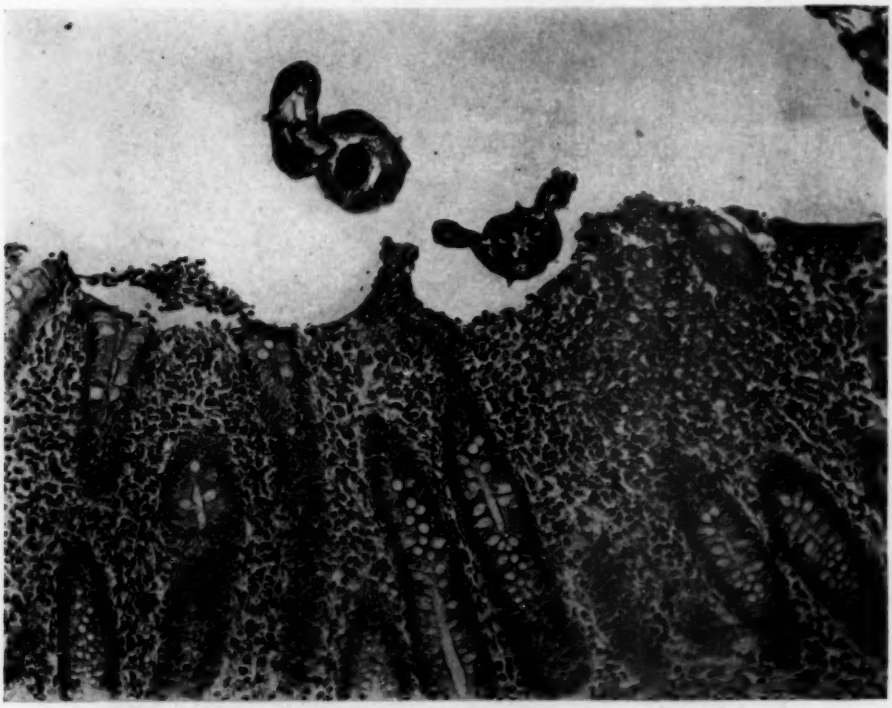

Fig. 2.—Two small mucosal erosions with the causal oxyurids. Hemalum and eosin stain; × 75.

smooth-walled defects without any evidence of reaction or of hemorrhage, although the winding channels made by the migrating worms are evident (figs. 4 and 5).

The two types of defects described, which are known to be produced by the worms, must be differentiated from technical artefacts. One of the most common of these artefacts is a large gaping space between the mucosa and the musculature. This artefact, produced by surgical trauma, occurs with equal frequency in appendixes containing oxyurids and in those free from them. Sometimes the oxyurids are found in

large numbers in such spaces, and individual worms may be found embedded in the tissue débris (fig. 6). Attention is directed to such defects to emphasize the fact that the oxyurids play no part in their production.

The lesions described have aroused considerable controversy. Rheindorf [5a, b, c] failed to distinguish between the first two types of defects.

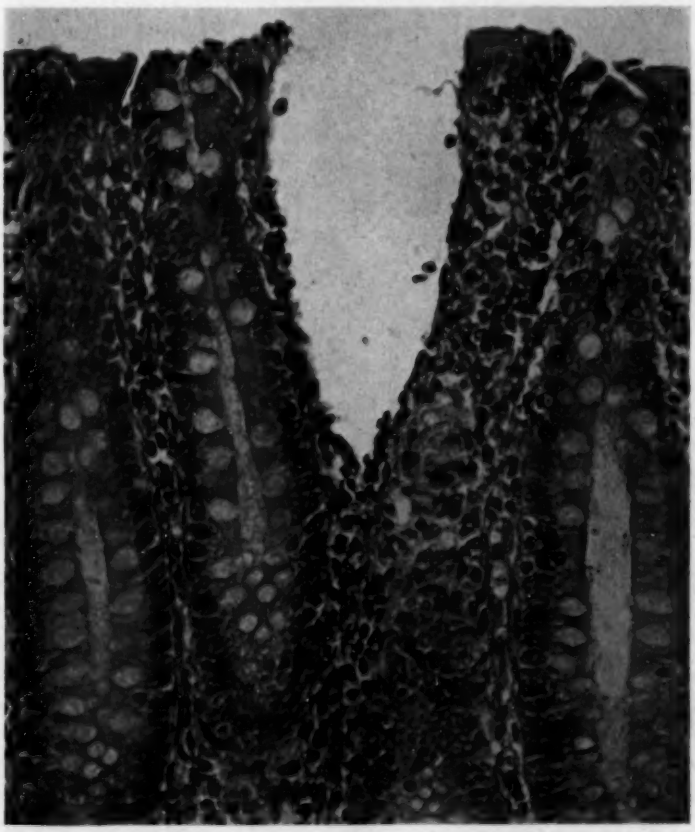

Fig. 3.—Mucosal defect with characteristic smooth walls and without hemorrhage or tissue reaction. The portal of entry for postoperative migration. Hemalum and eosin stain; × 100.

He warned against the dangers of secondary bacterial invasion when the defects are present. He believed that penetration into the submucosa and the lymphoid tissue is a common phenomenon. If this were true, one would expect the ingestion of blood by the worms, but in my material only an occasional parasite was seen with red blood cells in its intestinal tract. This finding is sufficiently rare to make it unlikely that oxyurids are thereby responsible for undernutrition, as has been claimed

by Rheindorf.[5d] Garin [16] suggested that the parasites are able to digest the epithelium of the appendix, but I found no evidence of this. Harris and Browne [20] and Cecil and Bulkley [22] also reported oxyurids in the wall of the appendix, and described small hemorrhages and necrotic lesions at the site of penetration. Aschoff,[6c, d] Hueck [7] and Brauch,[8]

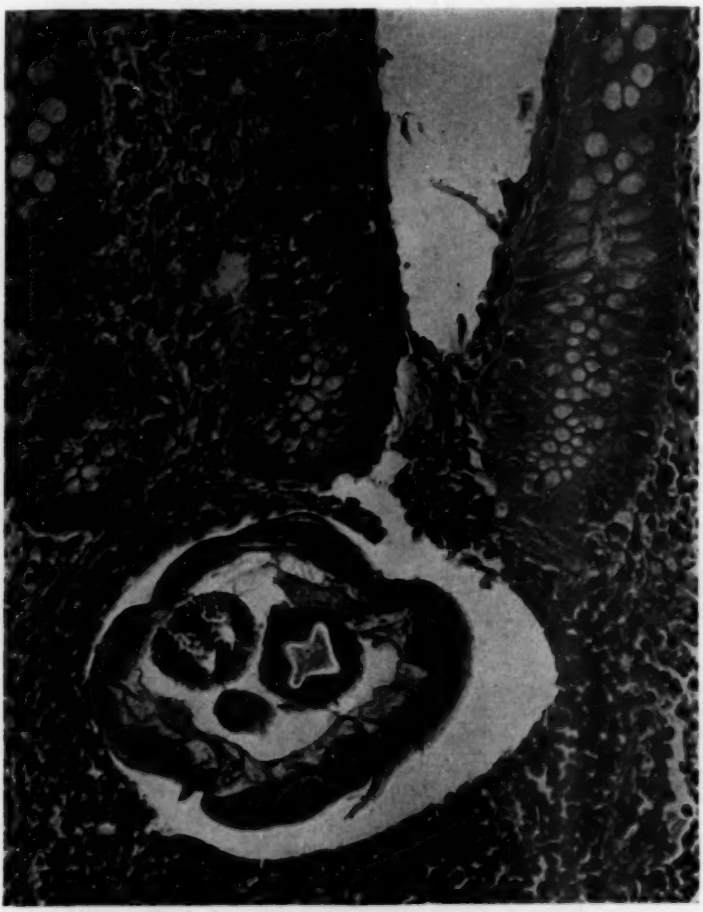

Fig. 4.—The winding channel leading from the mucosal defect seen in figure 3. The causal worm is in the submucosa. Hemalum and eosin stain; × 100.

on the contrary, insisted that both the small mucosal lesions and the larger defects are artefacts, in part due to operative trauma, and in part to impregnation with paraffin. Brauch claimed that impregnation with paraffin is always accompanied by artefacts, with more or less injury to the mucosa. Aschoff,[6c] however, modified his earlier stand [6a] as to the frequency and significance of appendical oxyuriasis. At first he

dismissed oxyuriasis as of consequence to the host, but later admitted the ability of oxyurids to penetrate the tissues. He noted the characteristic smooth-walled defects and the winding passages without reaction or hemorrhage. For this group he [6c] suggested the term "appendicopathia oxyurica," having in mind the production of pain and yet the

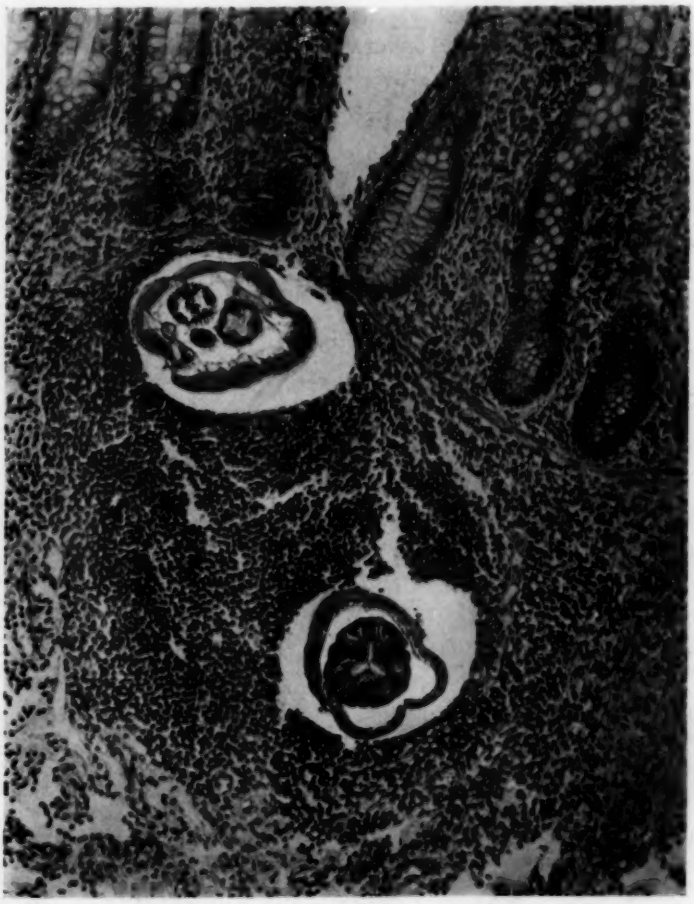

Fig. 5.—The channel seen in figure 4 leads into a lymphoid follicle with an oxyurid in situ. The passage and defect are smooth-walled, and there is no hemorrhage or inflammation. Postoperative migration. Hemalum and eosin stain; × 75.

absence of inflammation. Suzuki [23] considered some, but not all, of the defects described by Rheindorf as of the nature of artefacts. Contrary to Aschoff, he found small traumatic hemorrhages about the passages made by the worms. These hemorrhages were present in appendixes removed at operation and absent in appendixes removed post mortem.

He explained the difference on the basis of reduced motility of the worms in the latter, and suggested the term "appendicopathia oxyurica traumatica" for the condition as found associated with hemorrhages.

A more satisfactory explanation than any found in the literature offers itself to account for the defects of the second type in my description, namely, the presence of oxyurids in the appendical wall. Since none of my sections showed hemorrhage or reaction about the worms in the lymphoid tissue of the submucosa, I am forced to conclude that

Fig. 6.—Oxyurids at the site of an artefact due to operative trauma. To the left of the lower worm there is a small amount of fecal débris. Note the nuclear clumping in the submucosa and the absence of inflammation. Hemalum and eosin stain; × 100.

penetration occurred subsequent to operation. Only this theory of postoperative migration explains all of the observations of previous investigators as well as mine. Not only does it explain the otherwise insurmountable difficulty of complete lack of hemorrhage, but it also makes clear why no one has ever proved the production of inflammation by the carrying of bacteria from the appendical lumen into the tissues in or on the bodies of the worms. Likewise it explains the paucity of

observations of encysted worms or of foreign body reaction about necrotic worms in the appendical wall, my large material affording but a single doubtful example of this. The presence of the winding channels rules out artificial implantation. This postoperative, or at times postmortem, migration probably finds its explanation in the attempts of the worms to escape from a changing environment as the appendix cools, its p_H changes or the fixing fluid begins to penetrate into its interior. (Experimental investigation of the soundness of this theory is now being undertaken.) If it is physically possible for the worms to migrate into the tissues after operation, the possibility remains that they may do so before operation, but no example of this was found in my material. If such preoperative migration ever occurs, it must be exceedingly rare.

Incidence of Catarrhal Reaction: Still [3] first suggested a special type of catarrhal response to invasion of the appendix by oxyurids. Many writers have corroborated this finding. In my series the degree

TABLE 2.—*Degree of Catarrh in Relation to Oxyurids*

Degree	Appendixes Containing Oxyurids	Control Group
0	14 (4.5%)	6 (4%)
±	104 (33.4%)	54 (36%)
+	104 (33.4%)	56 (37.3%)
++	89 (28.6%)	34 (22.6%)

of catarrh was evaluated on the basis of the amount of mucin and the number of goblet cells. The results are expressed in four grades of severity (table 2). Only for the group graded ++ is the term "catarrhal appendicitis" applicable. A control group of 150 appendixes removed surgically from patients of similar age and sex as those from whom the oxyurid-containing appendixes came was studied with the same criteria in mind. As appears in the table, the results do not lend support to the concept of a catarrhal type of appendicitis caused by oxyurids. Appendical catarrh is dependent on general as well as on local conditions in which the oxyurids do not necessarily play an important part.

Response of the Lymphoid Tissue.—Lymphoid hyperplasia as a response to appendical oxyuriasis has been described by many writers (Rheindorf,[5c, e] Jaroschka,[26] Cecil and Bulkley,[22] Wood [29] and others). Jaroschka suggested that the lymphoid hyperplasia is an expression of the toxic effect of the worms. In assessing the degree of lymphoid hyperplasia in my material (table 3), attention was directed to the size and the number of follicles and to the appearance of the germ centers. The control group previously used was similarly evaluated. My find-

ings do not substantiate the claim that appendical oxyuriasis is attended by lymphoid hyperplasia of an unusual degree. Instead, the special degree of constitutional lymphatism is probably a much more important factor. If the host belongs to the thymicolymphatic constitutional group, the lymphoid tissue of the appendix shares in the generalized lymphoid hyperplasia characteristic of this constitution. The age of the host also is important. Other things being equal, the lymphoid tissues of children are functionally more active and anatomically larger than those of adults. Since oxyuriasis is particularly a disease of childhood, comparative series must be balanced as to age. Certainly Rheindorf's contention of lymphoid hyperplasia in a peculiar association with oxyuriasis, so marked as to lead to stasis in the appendix, cannot be substantiated. When such a degree of hyperplasia is present, it would

TABLE 3.—*Effects of Oxyurids on the Lymphoid Apparatus*

Observation	Oxyurids Present	Control Group
Follicles normal	149 (47.91%)	67 (44.6%)
Follicles atrophic	45 (14.47%)	24 (16%)
Follicles hyperplastic		
Slight	60 (19.29%)	23 (15.3%)
Marked	57 (18.32%)	36 (24%)

TABLE 4.—*Local Eosinophilic Response to Oxyurids*

Increase in Eosinophils	Oxyurids Present	Control Group
None	187 (60.12%)	82 (54.6%)
Slight	108 (34.73%)	58 (38.6%)
Marked	16 (5.14%)	10 (6.6%)

seem more reasonable to relate it to the constitutional make-up of the host. The studies of Drigalski and Koch,[13] who found a relatively high incidence of oxyuriasis in children of asthenic habitus, lend support to the constitutional concept, since the thymicolymphatic and asthenic constitutions are frequently associated.

Local Eosinophilia.—Several authors have investigated the degree of local eosinophilia accompanying appendical oxyuriasis, with varying results. My findings are summarized in table 4. The degree of eosinophilia was graded according to the average number of eosinophils in typical low power fields and according to the extent (depth) of infiltration. Comparison of the infested and control groups shows that local eosinophilia is not significantly increased on invasion with oxyurids. As with lymphoid hyperplasia and catarrh, so with local eosinophilia, the response is probably dependent on local and general factors and

independent of the parasites. While no certain relationship appears in this material between the degree of lymphoid hyperplasia and local eosinophilia, there is evidence to show that both are conditioned by the constitutional make-up of the host (Pende [37] and Macdonald [38]). Appendical eosinophilia is also in part dependent on the chronicity of the inflammation.

CLINICAL SIGNIFICANCE

While the frequency of oxyuriasis as reported for North America lags far behind the figures submitted from many of the European centers, the increasing incidence of infestation merits analysis in regard to its possible clinical import. A majority of the authors cited are agreed that oxyuriasis is of significance to the host. As mentioned, Aschoff [6c] suggested the term "appendicopathia oxyurica" for the painful morbid condition thought to be caused by oxyurids in some appendixes. He admitted penetration of the tissues by the worms, but denied that the mucosal defects are other than artefacts. Along with Hueck,[7] Brauch [8] and others, he made much of the fact that "appendicopathia oxyuria" is not accompanied by a high temperature. Rheindorf,[5b] on the other hand, noted a moderately high fever in some of his patients. Many surgeons, however, do not regard the fever as of value for the early diagnosis of appendicitis. Coller [39] expressed the belief that wa[illegible] ing for fever as a sign of acute appendicitis is dangerous. Aschoff [6d] and Hueck [7] suggested that the differentiation between true (primary) appendicitis and the pseudo-appendicitis of oxyuriasis is important, since the latter lends itself to correction by means of vermifuges and is not relieved by operation. Oppe [40] warned against the use of vermifuges, which call for purgation. Wood [29] noted certain differences between appendical oxyuriasis and appendicitis—a history of intermittent illness over a long period, absence of vomiting, slight leukocytosis, fever and "reflex nervous symptoms out of all proportion to the severity of the local lesion" being present in the former. He did not favor the use of anthelmintics.

With regard to the fibrosis so commonly seen in appendixes containing oxyurids, Rheindorf [5c] related the increase in connective tissue to the presence of the parasites. In favor of this view he cited the higher incidence of oxyuriasis in children over 6 years of age, compared with younger children. He suggested that the oxyurids may disappear after

37. Pende, N.: Constitutional Inadequacies, Philadelphia, Lea & Febiger, 1928.
38. Macdonald, I. G.: Ann. Int. Med. **6**:253, 1932.
39. Coller, F. A.: Personal communication to the author.
40. Oppe, W.: München. med. Wchnschr. **50**:859, 1903.

first causing mucosal lesions, and that the lesions gradually heal with the formation of scar tissue. This, in turn, favors kinking of the appendix, leading to severe appendicitis as a remote consequence of the infestation. Aschoff [6a, b] and Hueck [7] denied that oxyurids cause a sclerosing type of appendicitis, directly or indirectly. They considered the fibrosis a senile or an involutionary change.

The material under review does not lend itself to detailed clinical analysis. In table 5 are presented the pathologic diagnoses of the conditions in appendixes containing oxyurids. This table differs from a similar one appearing in a previous publication.[1] The latter showed the percentage occurrence of oxyuriasis for all the appendixes. The present table refers only to the 311 appendixes containing oxyurids. In none of the 71 appendixes showing active inflammation could the inflammation be attributed to the parasites. This claim is based on the fact that in these the worms were present only in the lumen, with no evidence of mucosal

TABLE 5.—*Pathologic Diagnoses Made on Appendixes Containing Oxyurids*

Diagnosis	Total	Percentage	Relationship to Oxyurids
Old recurrent appendicitis (no recent inflammation)	191	61.41	0
Active recurrent appendicitis	57	18.32	0
Recurrent, obliterating appendicitis	31	9.97	0
Active periappendicitis	18	5.78	0
Acute suppurative appendicitis	8	2.57	0
Acute purulent appendicitis	4	1.28	0
Acute gangrenous appendicitis	2	0.64	0

involvement. In no instance was there any sign of a more severe or advanced degree of inflammation at levels containing the worms than at levels free from parasites. Less direct evidence can be adduced by a statistical comparison of the appendixes without worms and those infested with oxyurids. Of the former, 26.37 per cent showed severe inflammation; of the latter, 22.85 per cent. Correction of the general operative group for age to correspond with the restricted age group favored by infestation with oxyurids yields a much higher incidence of severe inflammation (42.35 per cent). In the wall of an appendix the lumen of which contained oxyurids there was seen a granulomatous area made up of concentrically arranged fibroblasts and a few foreign body giant cells (fig. 7). The central portion of this granuloma contained a large oval calcified mass. Additional sections from the same block failed to show further trace of the area. While proof of its nature is not at hand, the possibility remains that it may have represented a dead oxyurid. The remainder of the appendixes containing oxyurids showed only old fibrosis with no evidence of recent inflamma-

tion, changes entirely comparable to those found in many appendixes without worms.

The term "appendicopathia oxyurica" possesses sufficient merit to warrant its retention, but it should be applied only when the appendix

Fig. 7.—Foreign body pseudotubercle containing oval mass of calcified material, with well marked fibroblastic reaction and a few giant cells about the foreign body. An unproved but probably encysted necrotic oxyurid. Hemalum and eosin stain; × 75.

shows evidences of intravital erosion or invasion. The mere presence of oxyurids in the walls of the appendix is not proof of etiologic significance. My material supports the view that oxyurids are not a significant cause of appendical pathologic changes.

CONCLUSIONS

1. The incidence of appendical oxyuriasis is increasing. Oxyurids were found in 311 of 26,051 (1.19 per cent) appendixes removed at operation. In the first 20,969 appendixes in this series, the incidence was 1.04 per cent.

2. Oxyurids occasionally cause minute mucosal lesions in the appendix. These lesions are accompanied by evidence of living tissue reaction: punctate hemorrhages, slight exudation and necrosis. The lesions occurred in 12 instances only; to this condition the term "appendicopathia oxyurica" may properly be applied.

3. In 256 instances the parasites occurred in the lumen of the appendix without producing visible lesions.

4. In 33 instances oxyurids were found in the wall of the appendix. Evidence is adduced to show that in this group penetration occurred after operation in every instance. This type of invasion is therefore of no pathologic or clinical significance.

5. No examples of appendicitis oxyurica occurred in my material.

6. Oxyuris vermicularis is not a significant cause of appendical pathologic changes.

SPONDYLITIS OF SWINE ASSOCIATED WITH BACTERIA OF THE BRUCELLA GROUP

WILLIAM H. FELDMAN, D.V.M., M.S.
Assistant Professor in Comparative Pathology, the Mayo Foundation
AND
CARL OLSON, JR., D.V.M.
Fellow in Comparative Pathology, the Mayo Foundation
ROCHESTER, MINN.

The widespread distribution of bacteria of the Brucella group among goats, cattle and swine, the not infrequent occurrence of undulant fever among human beings and the etiologic relationship of this disease to Brucella infections of animals constitute a public health problem of significance. The source of infection of undulant fever of man is often obscure, although there has been a popular tendency to incriminate the milk supply in many instances in which acceptable proof of the infectiousness of the milk was not presented. It is important, therefore, to keep in mind possible sources of infection other than that of milk.

In the last twelve months we have had an opportunity to study a spontaneous disease of swine characterized by the occurrence of spondylitis. From many of the lesions we isolated an organism of the Brucella group, which proved to be definitely pathogenic for certain laboratory animals.

SOURCE OF MATERIAL STUDIED

Our material, which consisted of specimens from twenty-four swine, was obtained from abattoirs under the supervision of the Division of Meat Inspection of the Bureau of Animal Industry of the United States Department of Agriculture. Although the exact locality from which the respective swine originated is not known, the majority of the animals from which lesions were obtained were raised in Iowa and Minnesota.

All the animals were subjected to competent antemortem inspection after their arrival at the respective abattoirs, and none manifested physical signs to suggest the presence of lesions found subsequent to slaughter. In fact, with the exception of an animal which before slaughter was observed to be affected with the granulomatous condition known as "scirrhous cord," all the swine were apparently normal and healthy, differing in no respect from the thousands of others slaughtered in the same period and found at necropsy to be without gross evidence of disease.

From the Institute of Experimental Medicine, the Mayo Clinic.

INCIDENCE

The condition which we have designated as spondylitis is by no means prevalent. Although it is not uncommonly seen in abattoirs in which large numbers of hogs are slaughtered daily, it is observed in only a small percentage of the total number of carcasses examined. We have little information concerning the incidence of the condition, but we have been able to secure some data that perhaps are of significance. Eleven of the specimens studied were obtained from one abattoir during a period when 67,000 swine were killed, thus suggesting that the disease may occur in one of approximately every 6,000 swine sent to slaughter from that part of the United States from which the animals with the lesions were obtained.

Since the lesions in the respective carcasses were observed near the end of the dressing process, when the identity of the respective viscera had been lost, it seemed desirable to obtain if possible a hog in which the infection might be demonstrated or at least suspected during life by the detection of specific agglutinins in the blood. If such an animal could be secured and properly identified before slaughter, a thorough necropsy might reveal some pertinent information and make available for additional study tissues which could not be obtained from animals killed and dressed by the routine procedure.

With this in mind, we arranged with one of the packing establishments to secure blood by tail bleeding from 102 apparently normal swine. The animals were from 8 to 10 months of age, and were selected at random from shipments of swine received from many different parts of Minnesota, Iowa and South Dakota.

Each animal was given an ear tag number, and after the blood was secured and before the animals were slaughtered, tests of agglutination were made. The results revealed agglutinins in the blood of one hog sufficient to cause agglutination of Brucella abortus antigen in a dilution of 1 : 25, whereas the blood of two other hogs caused incomplete agglutination at the same dilution. Although these titers are of questionable significance, the animals were carefully examined at necropsy, and many tissues were secured for the inoculation of guinea-pigs.[1] Lesions indicative of a specific infection were not recognized.

This phase of the problem should be investigated further, but the securing of blood from any considerable number of animals in stockyards and their retention during the time necessary to conduct a proper test of agglutination are formidable difficulties which would have to be met.

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1. These animals are still living.

PATHOLOGIC CHANGES ASSOCIATED WITH THE DISEASE IN SWINE

We have no evidence that sex or breed is of significance in the occurrence of the lesions. Females and castrated males were represented in approximately equal numbers in the twenty-four swine from which our specimens were secured. Material was obtained from only one boar. The age of the animals was comparable to the general average age of hogs slaughtered in the respective abattoirs. Of the eighteen animals the approximate ages of which were recorded, seventeen were between 7 and 12 months of age, and one was 3 years of age.

The lesions, which usually are situated in the lumbar vertebrae, were disclosed in the latter stages of the dressing process when the vertebral column was split longitudinally. Previous to this operation the viscera were removed from the body, and since these were without gross alteration the identity of the carcass from which they came was soon lost. As a consequence we were able to examine the liver and spleen from only one carcass from which the lesion in the vertebra yielded an organism of the Brucella group. In this instance the identity of the viscera was maintained on account of an unrelated pathologic condition elsewhere in the body.

The disease represents a definite pathologic entity occurring in the vertebrae of swine which during life do not exhibit physical signs of the disease, and which at necropsy are apparently without lesions in the parenchymatous organs. The infection manifests a characteristic predilection for the bony structure of the vertebral column, and it is revealed only when the spinal column is divided longitudinally (fig. 1 *A*).

Anatomically, the situation of the lesion in twenty-three of the twenty-four hogs was as follows: lumbar vertebrae, ten; last lumbar and first sacral vertebrae (lumbosacral articulation), eight; sacral, cervical and thoracic vertebrae, each one. In two animals the lesions were multiple and occurred in the thoracic, lumbar and sacral vertebrae.

The lesion was an irregular abscess in the body of the vertebra. We never observed the occurrence of a typical lesion which ultimately yielded an organism of the Brucella group in the bony structure dorsal to the spinal canal. Most of the necrotic foci seemed to originate in the vertebral epiphyses, often involving the articular cartilage and the epiphyses of the adjacent vertebral structure (fig. 1 *B*). The lesion usually consisted of a single focus, but occasionally instances were noted in which foci were multiple in the same or adjacent vertebrae, and in a few cases characteristic lesions were seen in various vertebrae, extending from the cervical to the sacral region.

It was often difficult to describe the shape of the respective lesions, owing to the irregular tortuous ramifications or sinuses by which the

morbid process extended into the body of the vertebral structure and in a few instances even penetrated the overlying musculature with subsequent formation of abscesses (fig. 2).

The lesions that occurred in the lumbar vertebrae, as most of them did, often extended to the dura mater, but actual penetration of this structure and subsequent involvement of the spinal cord were not observed (fig. 1 *B*). Occasionally, however, a lesion was encountered

Fig. 1.—*A*, spondylitis of a male hog, 1½ years old (case 11). The heavily encapsulated abscess involves the body of the last lumbar and the first sacral vertebra. An organism of the Brucella group was obtained from the spleen of a guinea-pig inoculated with a portion of an emulsion prepared from this lesion. *B*, spondylitis of a female hog, aged 9 months (case 5). The lesion has destroyed a portion of the intervertebral disk between two lumbar vertebrae. The jagged edges of the irregularly shaped cavitation extend in one place to the spinal dura mater. The necrotic contents of the lesion were removed for animal inoculations and the making of cultures. An organism of the genus Brucella was obtained by direct culture from this lesion and from the spleen of guinea-pigs.

the proximity of which to the spinal canal resulted in a slight bulging into the dural space, but the encroachment was never marked.

The size of the lesions was variable. They usually measured from 0.5 to 3 cm. in their greatest diameter. The contents of the respective cavitations, although somewhat variable in character, possessed certain common features. The contents were definitely necrotic, with some differences apparent in the character of the cellular detritus. The abscessed material was grayish white to slightly yellowish, and varied from a semipurulent or thick pasty consistence to a somewhat dry,

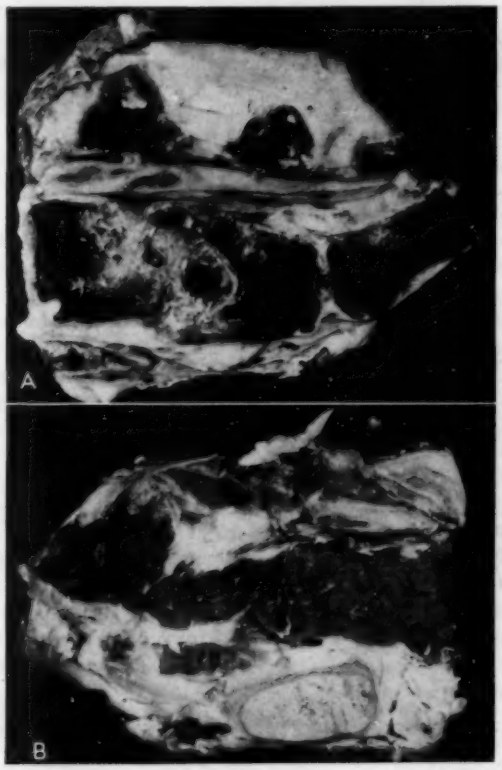

Fig. 2.—*A*, multiple lesions involving the bodies of the last two lumbar vertebrae (case 19). Much of the necrotic substance has been removed for cultures and inoculation of animals. Material from this lesion yielded bacteria of the Brucella group in direct culture, and induced lesions in guinea-pigs and rabbits. The morbid process extended bilaterally into the adjacent soft tissues. *B*, musculature adjacent to lesions of the vertebrae. The well encapsulated sinus, which is occupied by thick, creamy cellular detritus, communicates with the necrotic process affecting the vertebrae (same case as *A*).

caseous texture. Mineral salts were small in amount. Occasionally a lesion contained a sequestrum of bone.

The cavities were characteristically lined with a tough fibrous structure which provided a rather formidable encapsulation for many of the

abscesses. The capsular structure which was firmly adherent to the surrounding bone was most pronounced in the larger lesions, and frequently the walls were 0.3 cm. thick.

EXPERIMENTAL WORK

As the condition was encountered in different abattoirs, the diseased portion of the spinal column was removed for further examination. The procedure usually employed was as follows: The portion of bone containing the lesion was plunged into a pan of boiling water, in which it was permitted to remain for from three to five seconds.[2] The specimen was then removed from the boiling water, a pair of sterile sharp-pointed, curved scissors was thrust into the depths of the abscess, and as much of the material was evacuated as possible. Portions of the necrotic substance were used for the direct inoculation of culture mediums, and the remainder was used to prepare an emulsion for injection into animals.

CULTURE

In most instances from three to four tubes of the egg yolk agar medium described by Herrold[3] were inoculated for the isolation and growth of Mycobacterium tuberculosis and a similar number of tubes of a liver infusion agar prepared by slightly modifying the procedure described by Stafseth[4] and recommended by Huddleson.[5]

The tubes inoculated direct from the respective lesions were in most cases divided into two groups, and one group was incubated at 37 C. in a carbon dioxide

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2. This was done for the purpose of reducing the possibility of extraneous contamination. The time the specimens were permitted to remain in the boiling water was not sufficient to cause a perceptible elevation of temperature in the depths of the respective abscesses, so we do not think that the procedure was of significance in those instances in which subsequent cultural attempts and inoculations of animals gave negative results. On the other hand, the possibility for extraneous contamination of the exposed portion of the respective lesions was sufficiently great to warrant a procedure which would eliminate this factor if possible. That the method was efficient is attested to by the fact that few contaminated cultures were obtained.

3. Herrold, R. D.: J. Infect. Dis. **48**:236, 1931.

4. Stafseth, quoted by Huddleson, I. F.; Halsey, D. E., and Torrey, J. P.: J. Infect. Dis. **40**:352, 1927.

5. Huddleston, I. F.: Am. J. Pub. Health **21**:491, 1931. The liver infusion agar is prepared as follows: Solution 1. Two pounds (0.9 Kg.) of ground, fresh beef liver is put in a flask containing 2,000 cc. of distilled water and placed in the refrigerator overnight. Without removal of the liver infusion from the flask, it is autoclaved for one hour at 15 pounds (6.8 Kg.) of pressure. From 600 to 700 cc. of the fluid portion of the autoclaved liver infusion is filtered through several layers of gauze, and after the liquid is no longer warm, 500 cc. is permitted to filter through paper. Solution 2. This consists of bacto-agar, 20 Gm.; bactopeptone, 10 Gm.; sodium chloride, 5 Gm., and distilled water, 500 cc. The mixture is boiled for fifteen minutes, and solution 1 added. The total volume is brought to 1,000 cc., and the mixture is boiled for from two to three minutes. The p_H is adjusted to 6.8, and the mixture is placed in tubes and sterilized in an autoclave under 15 pounds of steam pressure for twenty minutes.

tension of 10 per cent, while the other tubes were incubated at the same temperature under atmospheric conditions. After the third day the tubes were examined at frequent intervals, and after eight or ten days if no growth occurred, they were discarded.

In almost all instances 1 cc. of the respective emulsions was also cultured for the presence of Mycobacterium tuberculosis. After treatment of the inoculum with 5 per cent oxalic acid, as suggested by Corper and Uyei [6] for the elimination of nonacid-fast bacteria, the material was seeded on four tubes of egg yolk agar proposed by Herrold.[3]

INOCULATION OF ANIMALS

With the exception of the material obtained from the first five cases, both rabbits and guinea-pigs were inoculated with portions of the respective emulsions prepared from the necrotic detritus secured from the different lesions. In the first five cases two guinea-pigs only were inoculated with material from each lesion, but in cases 6 to 24 inclusive, two rabbits were also inoculated. In cases 13 to 24 inclusive, three guinea-pigs were inoculated instead of two. Most of the guinea-pigs were males and were inoculated subcutaneously in the umbilical region. All the rabbits received the inoculum intravenously. The amount of emulsion injected into each guinea-pig and each rabbit was 1 cc.

The animals were permitted to live for eight weeks, after which they were killed for necropsy. At least forty-eight hours before being killed, all the guinea-pigs were given intracutaneous injections of avian and mammalian tuberculin, but in no instance was a significant allergic state elicited. At examination immediately after death, blood was secured directly from the heart for tests of agglutination,[7] and tissue, usually the spleen, was removed aseptically for the purpose of making cultures. Tissue was also secured for subsequent histologic examination. The tissues preserved were portions of the lungs, liver, spleen, both testes and in some instances the kidneys. All sections were stained to reveal the presence of acid-fast bacteria, and if significant lesions were present duplicate sections were stained also with hematoxylin and eosin.

RESULTS

By direct culture and from the tissues of the inoculated animals, organisms belonging to the genus Brucella were secured from ten of the twenty-four cases studied. A summary of the attempts of culture and of the inoculation of animals in the ten cases in which positive results were obtained is given in the accompanying table.

Few of the inoculated animals died before the expiration of eight weeks, and for the most part symptoms of diseases were not evident even though subsequent necropsy disclosed the presence of well established lesions. Although many of the infected guinea-pigs from which cultures of bacteria of the genus Brucella were isolated exhibited multiple characteristic focal lesions in the spleen and liver, in some

6. Corper, H. J., and Uyei, N.: J. Lab. & Clin. Med. **15**:348, 1930.

7. The antigen was prepared from several strains of Brucella abortus and was secured from the laboratory of Dr. C. P. Fitch of the University of Minnesota. The dilutions used were: 1:25, 1:50, 1:100, 1:200, 1:400, 1:1,000, 1:1,600, 1:3,200 and 1:6,400.

instances definite anatomic alterations as a consequence of the infections were not apparent.

Differences in the virulence of the inoculums were noted in several cases. Although definite histologic lesions were noted in the spleen of one guinea-pig (case 6) and a culture of Brucella organism was obtained from this organ, the other guinea-pig inoculated with an equal amount of the same emulsion as the first failed to reveal the slightest evidence of disease, and attempts to obtain cultures from the splenic emulsion

Summary of the Successful Attempts to Secure Organisms of the Brucella Group From Cases of Spondylitis in Swine

			Guinea-Pigs			Rabbits			
Case	Site of Lesion	Direct Culture from Abscess of Bone	Test of Agglutination	Lesions	Splenic Culture	Test of Agglutination	Lesions	Splenic Culture	Comment
5	Lumbar vertebra	+	0*	—	+	0	0	0	Splenic culture pathogenic for additional guinea-pigs
6	Not known	Not made	0	+	+	0	+	0	One guinea-pig failed to yield a culture
8	Lumbar vertebra	+	0	+	0	0	+	0	
11	Lumbar sacral articulation	Not made	+	+	+	—	—	—	Culture obtained from only 1 guinea-pig
12	Lumbar vertebra	Not made	+	+	+	+	+	+	
13	Thoracic vertebra	+	+	+	+	+	+	+	One rabbit gave positive agglutination, but failed to yield a culture
15	Lumbosacral articulation	+	—	—	—	—	—	—	Culture of low virulence
16	Lumbosacral articulation	+	+	+	+	+	+	+	Agglutination or lesions failed to develop in 1 of the 3 guinea-pigs; cultures negative
19	Lumbar vertebra	+	+	+	+	+	+	+	One of the guinea-pigs gave positive agglutination; culture was negative
21	Lumbosacral articulation	+	+	+	+	—	—	—	

* A zero indicates that data were not available.

were unsuccessful. In case 16, although marked lesions of Brucella infection developed in both rabbits and in two of the three guinea-pigs given injections of an emulsion prepared from the vertebral abscess, demonstrable lesions failed to develop in the third guinea-pig of the series. Agglutinins were absent, and cultures could not be obtained from the spleen. In case 21, in which a culture of the genus Brucella was obtained from the vertebral lesion by direct culture, neither of the two rabbits that were given injections of the emulsion prepared from material from the lesion possessed agglutinins when killed eight weeks after exposure; lesions were not observed grossly or microscopically, and the spleens failed to yield a positive culture.

The anatomic distribution of lesions of the experimental animals was seldom widespread. In guinea-pigs the organs of predilection were the spleen and the liver. The lungs were seldom affected, and gross alterations were not observed in the kidneys. On microscopic examination many of the male guinea-pigs were found to have purulent epididymitis; often this was not apparent to the unaided eye. The infection of the epididymis was usually bilateral, but in some cases the lesions were confined to one gland. On histologic study of the tissues, a few of the animals were found to have a specific epididymo-orchitis.

The lesions in rabbits were generally in the liver and spleen. Gross involvement of the lung was observed in one case. We failed to find lesions in the joints, lymph nodes, kidneys, testes or epididymis.

Briefly, the infection in guinea-pigs was characterized by enlargement of the spleen and the occurrence of focal lesions of variable sizes in the liver. Definite foci were not uncommonly absent in the spleen, and sometimes we succeeded in obtaining an organism of the Brucella group from the spleen, although the only abnormality demonstrable in this organ was slight hyperplasia. The lesions were most evident in affected livers, consisting of firm grayish-white foci, varying from areas of 0.05 cm. to elevated nodules averaging 0.3 cm. in diameter. The number of lesions ranged from few to many, and in those of the smaller miliary type the resemblance to certain experimental tuberculous infections, as mentioned by Fabyan,[8] was striking.

The spleen of infected rabbits was usually somewhat enlarged, but the presence of characteristic focal lesions was by no means consistent. When lesions were present in the spleen they were miliary, and usually measured up to 0.1 cm. in diameter. The involvement of the liver was likewise variable. Although as a rule a few focal alterations could be found in the liver of infected rabbits, occasionally necropsy revealed hundreds of lesions of the small focal or miliary type.

Microscopically, the character of the structure of the individual lesions was somewhat inconstant, depending on the duration of the infection and perhaps on the virulence of the respective bacterial cultures and their ability to overcome successfully the defense mechanism of animal tissue. The usual lesion consisted essentially of discrete, fairly well circumscribed collections of monocytic cells with a striking and characteristic tendency to assume an epithelioid appearance.[9] The respective collections of rather large lightly staining, diffusely arranged epithelioid cells comprising the individual lesions generally revealed a caseous-like central necrosis. Incomplete encapsulation, with the occurrence of

8. Fabyan, Marshal: J. M. Research **26**:441, 1912.

9. The histopathology of the lesions induced by the different organisms of the genus Brucella is to constitute the subject of a subsequent contribution; hence the description of the morphologic alterations is condensed in this paper.

many lymphoid and monocytic cells, was commonly observed, and a few giant cells were often present. Calcification was not observed.

In guinea-pigs, particularly in the epididymis and occasionally in the liver and lungs, a purulent abscess-like lesion developed which differed from the small or miliary lesion in that necrobiosis had progressed to a greater degree with a corresponding diminution of the number of epithelioid cells and more complete encapsulation of the lesion. In lesions of the epididymis such as these, many of the tubules of this structure often were filled with a purulent exudate which presumably had its origin in the infective foci in nearby tissues. The testicular structure was less often involved than was the epididymis, and the morbid process, when present, was of limited extent and seemed to have its inception in the interstitial portions of the gland. The apparent predilection of the infection for the epididymis makes it imperative to include this structure when the testis of the guinea-pig is to be examined histologically for lesions of experimental infection by an organism of the Brucella group.

All tissues preserved from the animal used in this study were stained to disclose the presence of acid-fast bacteria, but in no instance were organisms of this character seen.

IDENTIFICATION OF THE ISOLATED BACTERIAL CULTURES

The various bacterial cultures stained lightly with Loeffler's methylene blue (methylthionine chloride, U. S. P.) and gave a negative reaction to Gram's stain. The morphology was best revealed in preparations stained for from one to two minutes in Ziehl-Neelsen's carbolfuchsin, and examined without decolorizing. Generally the organism is best described by the term "coccobacillus." The presence of terminal granules in many of the bacteria was well brought out by the carbolfuchsin stain. Pleomorphism was commonly observed, the variation in appearance being particularly evident in the differences in size of the organisms within the same microscopic field. Many of the longer forms had a peculiar beaded appearance. Neither spores nor capsules were observed, and the bacteria were nonmotile.

Liver infusion agar slants or the egg yolk agar medium described by Herrold inoculated with material from lesions of spontaneous spondylitis usually revealed a growth in from two to four days. The growth appeared as numerous discrete, raised colonies, irregularly circular, each with a smooth glistening surface. After prolonged incubation the respective colonies became strikingly domelike, and as growth continued, there was a tendency for many of the adjacent colonies to become confluent, which gave the growth as a whole a pebbled appearance. This feature was most noticeable on the egg yolk agar medium. Chromogenesis was not observed, the growth remaining grayish to dirty white.

Subcultures of the organisms to agar slants resulted after incubation for forty-eight hours in a moderately abundant smooth slightly grayish, glistening filiform growth with slight elevation of the edges. Subcultures throve well in dextrose brain broth, with moderate clouding of the entire medium after incubation for seventy-two hours.

Using Meyer and ZoBell's [10] modification of the so-called dye test devised by Huddleson for the differentiation of the constituent members of the Brucella group, we found that the various strains isolated from the cases of spondylitis which we studied grew in the presence of thionine, 1:50,000, but growth failed in the mediums containing fuchsin, 1:50,000, and pyronine, 1:200,000. Consequently, the behavior of our strains in the presence of bacteriostatic dyes indicates that the organisms belong to that group of the genus Brucella known as the suis type. Additional evidence that the cultures we isolated were of the suis variety was obtained from the fact that a carbon dioxide tension was not essential for the isolation and subsequent growth of the respective strains. Although excellent growths were obtained on mediums incubated in the presence of 10 per cent carbon dioxide, growths of comparable degree were likewise obtained in cultures propagated under atmospheric conditions.

For the final identification of the respective strains of bacteria obtained from the lesions of the different swine, a study was made of their antigenic properties as revealed by their ability to stimulate the production of specific agglutinins in the blood of rabbits and guinea-pigs, and by their capacity to agglutinate in the presence of specific antibodies contained in the serum of cattle affected with Brucella abortus.

That specific agglutinins were produced in the various animals inoculated with respective emulsions of tissue was demonstrated by the fact that every animal from which a positive culture was obtained gave definitely positive agglutination when blood serum obtained at the time the animals were killed was added to a polyvalent Brucella antigen obtained from Dr. C. P. Fitch of the University of Minnesota. The blood of infected guinea-pigs gave an agglutination titer of 1:200 or more, whereas the agglutination titer of infected rabbits was 1:100 or more.

Suitable antigens were prepared from each of the respective strains of bacteria isolated, and the agglutinability of each was determined by the addition of graduated dilutions of blood serum obtained from a cow found to be a marked reactor to the test for agglutination of Brucella abortus. All strains of the bacteria obtained from the cases of spondylitis agglutinated in the presence of blood serum from this animal in titer comparable in most instances to the results observed when the antigen secured from Dr. Fitch was used.

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10. Meyer, K. F., and ZoBell, C. E.: J. Infect. Dis. **51**:72, 1932.

These observations pertaining to the biology of the micro-organisms obtained from abscesses of the vertebrae of swine, while in no sense comprehensive, are of sufficient significance, we believe, to justify the conclusion that the bacteria isolated belong to the genus Brucella and possess the salient characteristics usually attributed to the variety of the Brucella group known as suis.

SUPPLEMENTARY EXPERIMENTS

As the report of Krueger [11] indicated that organisms of the Brucella group could occasionally be isolated by inoculation of guinea-pigs from the lymph nodes of the mammary gland and from the diaphragmatic musculature of cattle supposedly infected with Brucella abortus on the basis of a positive test of agglutination, it seemed desirable to ascertain the possible infectiousness of certain tissues of swine in which lesions of spondylitis occurred. Additional tissues were therefore secured from seven of the carcasses of swine in which characteristic lesions of spondylitis were present. In the majority of instances the supplementary tissues emulsified for inoculation of guinea-pigs included portions of the muscle from the loin adjacent to the region of the lesion in the vertebra, muscle from one shoulder and bone marrow from one femur. In several cases portions of one kidney were emulsified, and in two cases inoculums were prepared from the inferior cervical and lumbar lymph nodes. In only one case was a portion of the diaphragmatic muscle secured for the inoculation of animals. From one hog portions of the spleen and liver were obtained, and attempts were made to demonstrate the presence of the specific bacterium.

Two guinea-pigs were each given injections of 1 cc. of the respective emulsions and were kept under observation for a period of eight weeks, after which they were killed and examined.

Specific agglutinins could not be demonstrated in the blood of any of the guinea-pigs used in this part of the study, and attempts to secure cultures of organisms of the Brucella group from the spleen failed in every instance. It should be noted, however, that cultures of the genus Brucella were obtained from the vertebral lesions of only three of the seven swine studied. Since the organism was not obtained from the four other animals either by direct culture or by inoculation of animals from what appeared grossly to be characteristic lesions of Brucella infection, it is hardly surprising that the infectiousness of apparently normal structures was not demonstrated.

COMMENT

Although we have no knowledge of the disease under consideration having been described previously, the occurrence of the lesions in the

11. Krueger, H.: Deutsche tierärztl. Wchnschr. **40**:481, 1932.

vertebrae of swine and their relationship to bacteria of the Brucella group were recorded in the annual report of the chief of the Bureau of Animal Industry of the United States Department of Agriculture for the year ending Sept. 8, 1930.[12] Brucella abortus of the porcine type was considered the causative agent of peculiar tuberculous-like lesions of the body of vertebrae which had been submitted to the federal laboratory from Philadelphia. The following comment was made: "Owing to the high virulence of the swine bacillus and its pathogenicity for man, these bone lesions have a special significance in meat inspection work." In the annual report of the same bureau for the year ending Aug. 31, 1931,[13] it was stated that it had been definitely shown that these lesions are due to micro-organisms of the Brucella group, and that additional material studied had brought the total number of specimens yielding the organism to twenty-two. In the report for the year ending Aug. 31, 1932,[14] the disease was again mentioned. Of 154 specimens that had been examined, sixty-five, or approximately 42 per cent, were found to contain viable strains of the genus Brucella. Specimens from which positive results were obtained were forwarded to the laboratory by representatives of the Federal Meat Inspection Service from cities in Minnesota, Iowa, Nebraska, South Dakota, Missouri, Florida and Massachusetts.

The exact geographic distribution of the disease is a matter of conjecture, since many swine slaughtered in one state originate in territory considerably removed from the abattoir. However, the finding of lesions in hogs slaughtered in such widely separated states as South Dakota, Florida and Massachusetts suggests that this specific type of Brucella infection is probably endemic in many different parts of the United States. What the relationship of the vertebral involvement may be to abortion disease of swine, which is an infection of the placental membranes resulting in the premature expulsion of the fetus, or to Brucella infection in other species is not known.[15]

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12. Annual Report of the Chief of the United States Department of Agriculture for the Year Ending Sept. 8, 1930, p. 55.

13. Annual Report of the Chief of the United States Department of Agriculture for the Year Ending Aug. 31, 1931, p. 54.

14. Annual Report of the Chief of the United States Department of Agriculture for the Year Ending Aug. 31, 1932, p. 42.

15. Another example of an extra-uterine infection of swine by organisms of the Brucella group was given by James and Graham (J. Am. Vet. M. A. **77**:774, 1930). They described a condition in one herd of swine in Illinois which apparently had persisted on the same premises for several years. The affected animals displayed symptoms of soreness or stiffness in walking, and distinct swellings of the front and hind fetlock joints were sometimes noted. A study of the disease revealed lesions of pyemic arthritis, pyemic bursitis and osteomyelitis from which bacteria of the genus Brucella were isolated. The existence of spondylitis in the animals studied was not mentioned.

It seems unusual that spondylitis of swine due to bacteria of the Brucella group should have been recognized as a definite entity only within a relatively recent period. The apparent similarity of the disease to lesions of the bones due to Mycobacterium tuberculosis may frequently have obscured the true character of the lesions. The absence of reports of Brucella infections of this character in continental Europe may also have been due to failure to distinguish the condition from lesions of tuberculosis. Nieberle,[16] in discussing tuberculous infection of the bones of domesticated animals, commented on the common occurrence of tuberculous lesions in the bones of swine in Germany, and pointed out that similar lesions were less often encountered in the bones of cattle. Nieberle mentioned that in tuberculosis of the bones of swine, the regional lymph nodes often are not diseased. These observations seem significant and suggest that perhaps some of the lesions which are considered by their gross appearance to be tuberculous are due to organisms of the genus Brucella.

An interesting example of the predilection of organisms of the Brucella group for osseous tissue was a case described recently by Kulowski and Vinke.[17] The patient was an American farmer, aged 33, who had been ill for several months. He complained of pain in the lower portion of the back, had lost much weight and had had several intermittent chills and fever. Tests for agglutination of Brucella were definitely positive, and this with the roentgenologic examination suggested a diagnosis of "Malta fever spondylitis." By surgical means an abscess situated in the lumbar region "in front of the right lower three transverse processes" was drained, and a culture of the bovine variety of Brucella was isolated. Kulowski and Vinke commented on the frequency of pain low in the back as an early symptom in patients affected with undulant fever, and said that "it is reasonable to assume that spinal involvement has been frequently overlooked in the past."

Our study affords only presumptive evidence that the respective strains of Brucella isolated from the different specimens were responsible for the osseous lesions. Conclusive proof of the causative relationship of the specific bacterium to the resultant spondylitis must await confirmatory experimental data. Experimental work of this character is in progress and will be reported later.

Although the etiologic significance of the bacteria obtained from the different lesions may not be definitely proved, the data so far obtained in support of this contention seem convincing. The character of the lesions, the low incidence of the disease and the endemic nature of

16. Nieberle, K.: Pathologische Anatomie und Pathogenese, Ergebn. d. allg. Path. u. path. Anat. **25**:631, 1931.

17. Kulowski, J., and Vinke, T. H.: J. A. M. A. **99**:1656, 1932.

Brucella infections of swine are factors which suggest a specific etiology, with bacteria of the Brucella group the most likely culprits.

Failure to demonstrate a viable organism of etiologic significance in all of the specimens is not surprising when one considers the pathology of the disease. The lesion usually represents a more or less chronic, nonprogressive type of infection that is rather self-limiting, by virtue of the encapsulation which ensues. A structure of this kind hardly provides an optimal environment for the residence of bacteria in a living, pathogenic state, regardless of the tenacity of the micro-organisms in question. The appearance of most of the lesions studied gave a definite impression of chronicity. The duration of the respective abscesses is not known, but it is not unlikely that the majority represented a process that had its inception many months before the animal was killed. The semidry contents of some of the more thickly encapsulated lesions would certainly indicate such duration. The characteristic encapsulation of the lesion of spondylitis of swine associated with bacteria of the Brucella group may account for the failure of lesions to develop in parenchymatous organs such as the liver and spleen.

The evidence would suggest a hematogenous infection as responsible for the inception of the osseous lesions, although the explanation of the apparent predilection of the infection for the vertebrae of the lumbar and sacral region is not obvious.

Our experience indicates that those lesions which contain viable bacteria will yield the organism by direct culture on suitable mediums as consistently as by the more protracted and complicated procedure of isolation from the tissues of guinea-pigs previously given injections of the infective inoculums. Of course, when it is desirable to know something of the pathogenicity of the bacteria, animals must be inoculated. The inoculated animals also provide in positive cases agglutinins which are of much value in identifying the specific infection by the aid of serologic procedures.

SUMMARY AND CONCLUSIONS

A specific spondylitis of swine associated with bacteria of the genus Brucella is described. Lesions were obtained from twenty-four different animals, and organisms of the Brucella group were secured by culture and by inoculations of animals from ten. The identity of the respective cultures was determined by their behavior in experimental animals and by their antigenic properties.

The affected swine were apparently symptomless and without lesions in other parts of the body. The lesion was an encapsulated, abscess-like structure occupying an irregular cavitation in the body of the vertebra. The disease exhibited an apparent predilection for the vertebrae of the lumbar and sacral region, and adjacent vertebrae were frequently

involved. The majority of the specimens obtained were from animals less than 1 year of age, and a relationship of the lesions of the vertebrae to the usual lesions of infectious abortion in swine was not observed.

The presence in many of the necrotic foci of the vertebrae of swine of bacteria of the genus Brucella, which have a proved pathogenicity for guinea-pigs and rabbits, provides a possible source of infection for farmers, packing house employees, retail butchers and others who may handle pork in an uncooked state.

Dr. D. D. Tierney, Dr. George E. Totten and Dr. John L. Myers of the Meat Inspection Division of the Bureau of Animal Industry, United States Department of Agriculture, assisted in obtaining the vertebral lesions utilized in this study.

INFLUENCE OF THE INTAKE OF CALCIUM ON THE THYROID GLAND OF THE ALBINO RAT

JUANITA THOMPSON, M.D.
TORONTO, CANADA

The present study was undertaken for the purpose of determining the influence of the intake of calcium on the thyroid gland of the albino rat under specific conditions. The theory that an excess of calcium, either sulphate or carbonate, in the drinking water derived from geological formations rich in this element is an etiologic factor in the production of goiter [1] was advanced prior to the present conception of the relationship between iodine deficiency and this condition.[2] Although considerable experimental evidence has accumulated to support the hypothesis of iodine deficiency, few contributions justify the earlier view. Certain observations are not in accord with either conception. Since a high incidence of goiter has been found in areas where iodine is considered to be abundant,[3] and relatively few in certain limestone regions where the drinking water is turbid with suspended lime,[1d] both opinions have been challenged.

The possibility of an interrelationship between calcium and iodine in the development of goiter was suggested by geologic studies on the distribution of iodine. Von Fellenberg [4] pointed out that iodine tends to be leached out of soil rich in calcium. From such formations he obtained a relatively greater number of low quantitative values for iodine. On this basis it would seem reasonable to assume that the intake of people living on similar formations would not only be low in iodine, but high in calcium. Goiter occurring in such a district would be associated with an imbalance between these two elements. On this

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From the Department of Medical Research, Banting Institute, University of Toronto.

1. (*a*) Berry, J.: Diseases of the Thyroid Gland, Philadelphia, P. Blakiston's Son & Co., 1901; (*b*) Lancet **1**:269, 1926. (*c*) Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 8, p. 436. (*d*) Orr, J. B., and Leitch, I.: Iodine in Nutrition, Medical Research Council, Special Report Series, no. 123, London, His Majesty's Stationery Office, 1929.

2. (*a*) McClendon, J. F., and Williams, A.: Proc. Soc. Exper. Biol. & Med. **20**:286, 1922-1923. (*b*) Marine, D.; Lenhart, C. H.; Kimball, D. P., and Rogoff, J. M.: The Prevention of Simple Goitre, Bull. Western Reserve Univ., 1923, no. 26. (*c*) Orr and Leitch.[1d]

3. Holst, J.: Klin. Wchnschr. **10**:118, 1931. Lunde, G.: Canad. M. A. J. **21**:337, 1929 (cited in editorial). Pern, S.: New York M. J. **115**:409, 1922.

4. von Fellenberg, cited by Orr and Leitch.[1d]

basis, the theories of iodine deficiency and excess of calcium in the production of goiter appeared to be correlated. It was hoped that some insight into this complex problem might be gained through the present investigation.

EXPERIMENTAL OBSERVATIONS

Rats were placed in roomy wire cages with mesh bottoms, 5 animals to a cage. The cages were frequently washed and sterilized. No bedding was used. Clean coarse pine shavings were kept in the underlying trays.

Although a number of investigators [5] have emphasized the difficulties arising from contamination of food in dietetic studies of goiter, adequate stress has not been given to the importance of segregating the animals on the low from those on the high iodine diets. Since the amount of iodine required by the rat is very small, minute traces of this element in the environment may exert considerable influence. For this reason, the majority of the animals receiving additional iodine in their food were kept in separate and remote quarters. A small number of rats on low iodine diets were housed in the same room with animals on high iodine diets, to test out this assumption.

The basic diet consisted of 76 parts of ground yellow corn, 14 parts of wheat gluten, 6 parts of wheat germ, 1 part of chemically pure sodium chloride, 1 per cent of 1 D viosterol [6] and distilled water. Supplementing this diet, approximately 1 cc. of tomato juice per rat per day was given to render the vitamin content adequate. By analysis this food was found to contain approximately 0.003 mg. of iodine and 0.08 Gm. of calcium per hundred grams. It was employed either alone or modified by the addition of 3 per cent of chemically pure calcium carbonate or of 0.00128 Gm. of potassium iodide per hundred grams, or by a combination of both. As much food and water as the animals would voluntarily consume was given.

For the purpose of the present experiment the diets were considered to have four primary combinations: (1) low calcium-iodine content, (2) low calcium plus iodine, (3) high calcium-low iodine, (4) high calcium plus iodine.

The animals were placed on these diets at 1 month of age. A number were killed at monthly intervals, beginning at the end of the second month. The experimental period extended from December, 1931, to July, 1932.

After the desired interval had elapsed, the animals were etherized. They were incompletely exsanguinated by bleeding from the great vessels of the neck. Immediately following this procedure, the thyroid glands were secured, grossly examined and placed in a diluted solution of formaldehyde, U. S. P. (1:10). This routine excluded the possibility of postmortem changes. After adequate fixation, paraffin sections were made. Hematoxylin and eosin staining was used.

RESULTS OF STUDY

After having examined the entire series of histologic preparations of the thyroid glands from the rats, it was found necessary to develop

5. (*a*) Bourget, G. E.: Am. J. Physiol. **44**:492, 1917. (*b*) McCarrison, R.: Simple Goitres, New York, William Wood & Company, 1928. (*c*) McCarrison, R., and Madhava, B.: The Life Line of the Thyroid Gland, Calcutta, India, Thacker, Spink & Co., 1932.

6. In these studies, 1 D viosterol was obtained by diluting 250 D viosterol with the requisite amount of corn oil.

a classification in order to interpret the findings logically. Four major divisions were recognized: (1) the normal, (2) the hyperplastic, (3) the transitional and (4) the atrophic.

A typical microscopic section of a nonhyperplastic or normal thyroid gland showed it to be composed of moderate-sized acini having a rounded contour. Irregularly interspersed throughout were alveoli which varied in size and shape. These glandular elements were supported by a delicate connective tissue stroma. The vessels were not

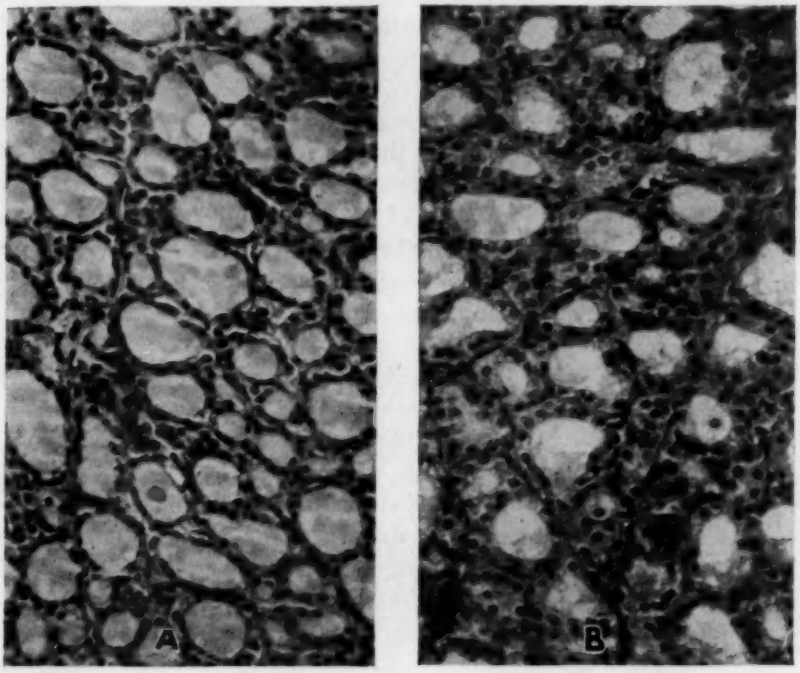

Fig. 1.—*A*, nonhyperplastic thyroid of rat receiving iodine. *B*, thyroid showing slight hyperplasia; low calcium-low iodine diet.

injected. The colloid content of the vesicles varied. The lumens of the large follicles and those of the majority of the moderate-sized follicles were entirely filled by dense bland homogeneous colloid. In others the colloid was transparent and granular. Occasionally the colloid formed a crescentic mass, occupying one side of the acinar space. It was indistinguishable in a few of the small alveoli. Slight peripheral vacuolization was observed. The epithelial cells lining the acini containing the greatest amount of colloid were very flat. Their cytoplasm was acidophilic and coarsely granular. A meager amount surrounded the intensely stained elongated nuclei. A change in the height of the

cells was noted in follicles containing lesser amounts of colloid. In a number of these follicles the lining cells became cuboidal. The cytoplasm of these cells appeared more abundant. Their nuclei were rounded and frequently showed a coarse reticular structure. A clear halo of variable size surrounded many of the nuclei. It was difficult to define the internal border of the epithelial cells in some of the alveoli, since their cytoplasm appeared to merge with the colloid content.

The microscopic appearance of the thyroid sections showed very little change with increasing age. In older animals the supporting connective tissue had an increased collagenous content. As a result, the lobular divisions were discerned more readily.

The various sections differed from one another with respect to the size of the predominating acini, the prominence of the lobular divisions, the amount of stainable colloid, the degree of vacuolization and the number of interacinar, undifferentiated cell groups. Nevertheless, despite this variability, the height of the epithelial cells never progressed beyond the low cuboidal variety; the colloid content of each section was abundant, and vascular injection was absent. These features were considered the essential requirements for placing a gland in the normal or nonhyperplastic group.

It is a known fact that the development of any pathologic abnormality is a gradual process, the stages of which blend with one another. On this basis, glands affected by hyperplasia were arranged in order of the degrees of microscopic change. The gradations were classified as slight, moderate or marked. Since each group consisted of a series of transitions characterized by a number of outstanding common features, the boundaries of individual groups were indefinite. This particular feature made the correct placing of certain specimens doubtful.

The slightly hyperplastic group was composed of glands in which there was relatively little deviation from the normal microscopic structure. On section, hypertrophy of the majority of the alveolar cells to a high cuboidal type of epithelium was noted. This was associated with a decrease in the colloid content. There was a moderate degree of vascular injection. In most of the sections the formation of new vesicles was apparent. These vesicles appeared to be arising from interacinar accumulations of undifferentiated cells.

Glands presenting hyperplasia of a moderate degree differed from the preceding group in that many of the alveoli had lost their regular contour. Small plications of the alveolar walls were frequently observed. The colloid content was greatly depleted. It was lacking from the majority of the follicles. The colloidal remnant appeared either thin, granular and vacuolated or as a network of coarse, irregular strands. Vascular injection was more conspicuous.

The markedly hyperplastic group consisted of glands in which there was a greater degree of microscopic change. The majority of sections showed the glands to be composed of enlarged acini. The acini were very irregular in size and shape. Papillomatous ingrowths were numerous. The alveoli appeared to be increased in number. It seemed probable that this increase had resulted either from papillary fusion or from budding. Stainable colloid had completely disappeared. The majority of the epithelial cells were columnar. Their cytoplasm was increased in amount, acidophilic and finely granular. The round or oval finely

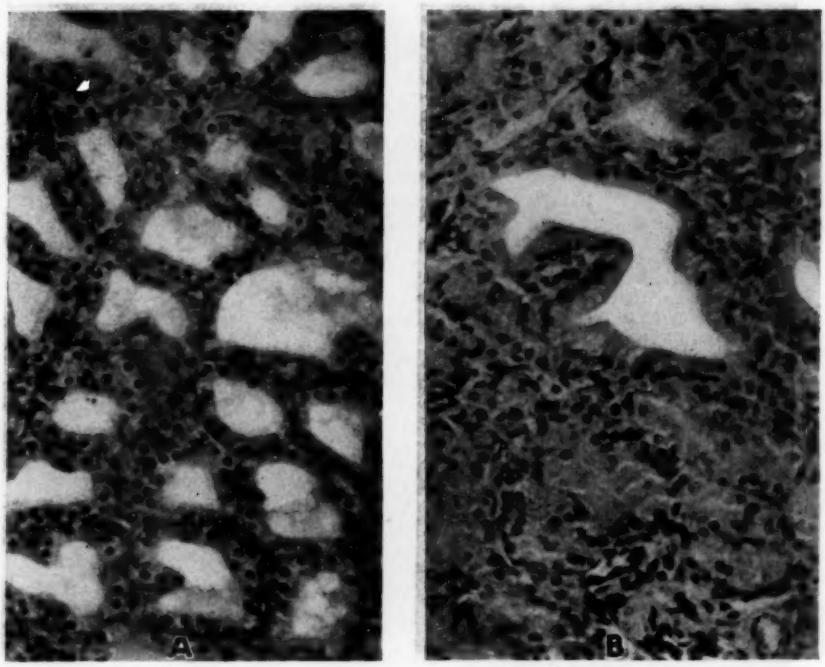

Fig. 2.—*A*, thyroid showing moderate hyperplasia; low calcium-low iodine diet. *B*, thyroid showing marked hyperplasia; high calcium-low iodine diet.

reticular nucleus varied in size. It usually occupied a central position within the cell. The internal border of the epithelial cells was frequently indistinct; numerous mitoses were seen. The vascular channels were greatly engorged.

From the microscopic appearance of the glands studied, it was difficult to follow with any certainty the sequence of changes from the stage of hyperplasia to that of atrophy. The transitional stages were characterized by changes in both the follicles and their content. Frequently the acini were formed by degenerated epithelial cells. Enlargement was not unusual. In a number of sections meager amounts of

colloid reappeared in many of the alveoli. In some of the glands these changes were of patchy distribution.

In the majority of the thyroid glands atrophy was associated with a complete transformation in the microscopic picture. The atrophic glands showed gradations in the degree of microscopic change, as did the hyperplastic group. They fell into two groups: the early and the late atrophies.

Glands considered as showing early atrophy had completely lost their orderly structural arrangement as the result of a complete or a

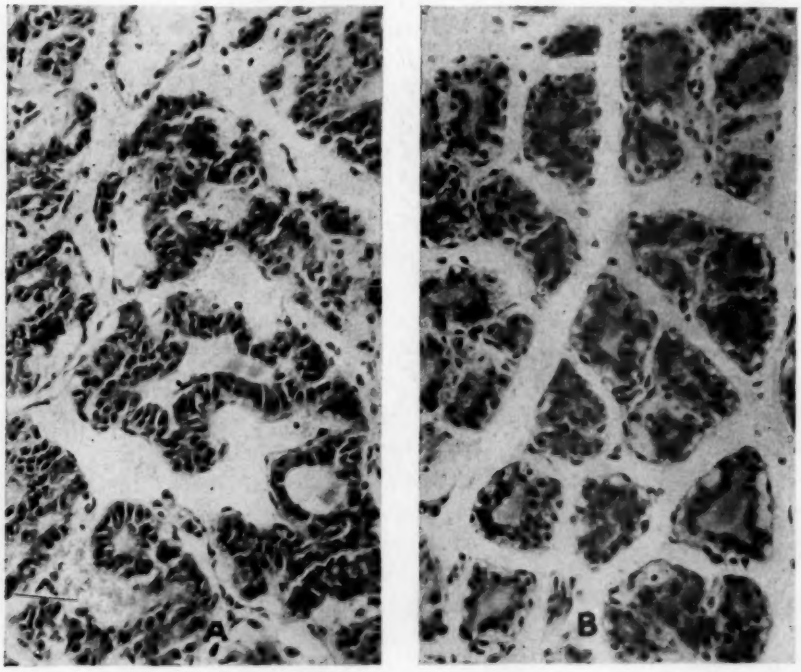

Fig. 3.—*A*, thyroid showing early atrophy; high calcium-low iodine diet. *B*, thyroid showing late atrophy; high calcium-low iodine diet.

partial collapse of the follicular structures. The epithelial elements formed irregular cords, groups or distorted acini. The previously hyperplastic alveolar cells had undergone profound degenerative changes. The nuclei appeared diversiform and intensely pyknotic. They were irregularly placed within shrunken, deeply stained cytoplasm. The cellular outlines were poorly defined. Frequently slight separation of the cells was noted. In the partially collapsed alveoli, nonvacuolated, homogeneous, dense colloid was present. Since the supporting stroma had not contracted with the follicular collapse, it was seen more readily. The vascular bed was engorged.

In contrast to the early stage, late atrophy presented a bland appearance. The distorted acini were reduced in size. The majority of the epithelial columns and cellular groups had disappeared. The remaining epithelial cells appeared to be of a similar degenerative character. Most of the acini contained quite dense, nonvacuolated colloid. The vascular turgescence had subsided.

In order to avoid any personal inclination involved in evaluating the preparations, they were first arranged according to the foregoing classification, without knowledge of the experimental group to which a specimen belonged. This relationship was later determined.

From the results indicated in table 1 it will be seen that hyperplastic thyroid glands were found in 67 per cent of 24 animals maintained on the low calcium-low iodine diet for a period of two months. In 54 per cent of these the degree of response was slight, and in 13 per cent it was moderate. The remainder of the glands were considered within

TABLE 1.—*Changes in the Thyroid Gland Occurring in Rats on Low Iodine Diets*

			Changes in Thyroid Gland						
				Hyperplasia				Atrophy	
Diet	Time on Diet, Mos.	Number of Animals	Normal, per Cent	Slight, per Cent	Moderate, per Cent	Marked, per Cent	Transitional, per Cent	Early, per Cent	Late, per Cent
Low calcium.....	2	24	33	54	13	..	....	....	....
High calcium.....	2	35	..	..	9	91	....	....	....
Low calcium.....	3-7	33	..	..	6.1	..	72.7	9.1	12.1
High calcium.....	3-7	35	..	..	..	56.6	17.1	17.1	8.5

the normal range. In contrast, 100 per cent of the group of 35 animals on the high calcium-low iodine diet had hyperplastic glands. Not only were all the glands hyperplastic, but the response was excessive in comparison with that in the preceding group on the low calcium diet. Marked changes were found in 91 per cent of these. A lesser degree of response was shown in the remaining 9 per cent.

Retrogressive changes became manifest in a number of specimens obtained at the end of the third month from animals on low iodine regimens. Ninety-three and nine-tenths per cent of 33 animals on the low calcium-low iodine diet and 43.4 per cent of 35 animals on the high calcium-low iodine diet showed these pathologic abnormalities throughout the experimental period. The percentage difference between the groups on the low iodine diet was due to the persistence of hyperplasia in rats receiving additional calcium. Since transitional phases of the retrograde phenomena affected the majority of animals on the low calcium-low iodine diet, it seems that the conditions in this group favored regression. Conversely, in the group on the high calcium-low iodine diet, the prerequisites tended to retard the onset of similar manifestations.

Attention has previously been directed to the difficulty of following the consecutive microscopic stages in the transformation from hyperplasia to early atrophy. Following the careful examination of sections placed in the transitional group, the occurrence of certain trends in the response of the animals on the same diet was indicated. The essential difference between the two groups was related to the reappearance of colloid in rats on the low calcium-low iodine diet. In these specimens, small amounts of thin colloid were observed within the lumens of some of the hyperplastic follicles situated in the periphery of the sections. Nuclear and cytoplasmic degenerations developed secondarily in the follicular epithelium. The amount of colloid observed was considered inadequate to prevent the later acinar collapse.

Aside from the foregoing changes, another type of reaction was observed in a number of specimens from animals that had been on the same diet for from five to seven months. Thin granular colloid appeared in a considerable number of the alveoli the epithelial cells of which showed little hypertrophy. In one of the oldest specimens, this accumulation had been focal, microscopically resembling an adenoma. In contrast, the earliest retrograde phenomenon recognized in glands from animals on the high calcium-low iodine diet was the presence of small groups of enlarged acini lying in the periphery. These follicles were formed by degenerated epithelial cells having pyknotic nuclei of variable size embedded in intensely stained, shrunken cytoplasm. In some of the sections, similar cellular degenerations were observed in alveoli of the usual size. Infrequently small amounts of stainable colloid were seen within the lumens of these acini.

Approximately the same number of atrophic glands were found in both groups of animals on low iodine diets. The two groups differed, however, in the degree of atrophy. In rats on the low calcium-low iodine diet, early and late atrophy appeared with about the same frequency. A relative increase in the early atrophic lesions was shown in the group on the high calcium-low iodine diet. No correlation existed between the degree of atrophy found in glands from animals within the same experimental group and the duration of the deficiency.

The thyroid glands of 106 animals on similar diets supplemented by potassium iodide were examined at corresponding monthly periods. These glands invariably had a nonhyperplastic structure. No increase in the colloid content was demonstrable in the glands of animals on the high calcium diet with added iodine.

In planning the work, the importance of widely separating rats on low iodine diets from others receiving supplemental iodine was considered. The findings recorded in table 2 showed that diets capable of producing marked hyperplasia of the thyroid gland in the majority of

segregated animals gave rise to decreased or irregular reactions in the nonsegregated group. From these results it is evident that many of the latter group were acquiring additional iodine. The source was either from a certain amount of sublimation from the food with a high iodine content supplied in open dishes in nearby cages or through inadvertent contamination. These observations suggest that a low intake of iodine can be relied on only in animals widely separated from others receiving iodine in their diets.

After having made a careful histologic survey of the various specimens, the question arose concerning the relationship of these findings to the macroscopic appearance. In the gross, the normal or nonhyperplastic glands were small and pale pinkish gray. The isthmus was usually indistinct. With increasing cellular activity the glands gradually enlarged and assumed a dark grayish-pink color. The isthmus was readily seen. The small superficial ramifications of the vascular chan-

TABLE 2.—*Influence of Segregation on the Initiation of Changes in the Thyroid Glands of Rats on Similar Diets*

Number of Animals	Time on Diet, Months	Conditions	Changes in Thyroid Gland				
			Normal, per Cent	Slight, per Cent	Moderate, per Cent	Marked, per Cent	With Colloid Retention, per Cent
21	2	Not segregated	9	38	14	14	25
35	2	Segregated	..	..	9	91	..

nels began to appear. Grossly, glands presenting microscopic evidence of marked hyperplasia were greatly enlarged and a deep congested red. Their surfaces frequently appeared finely granular. Greatly engorged, tortuous vessels stood out like whipcords on the gland. The isthmus appeared as a thin dark red band. The thyroid tissue was quite friable. The atrophic glands had a macroscopic appearance indistinguishable from either the hyperplastic or the normal groups. The atrophies classified as early could not be differentiated in the gross from changes graded as markedly hyperplastic. A gradual approach toward the normal macroscopic appearance became evident in glands in which there was microscopic regression toward the late atrophic state. Based on these observations, interpretation of the activity of the thyroid gland of the rat from the gross appearance alone should be made with caution.

COMMENT

Investigators concede that the thyroid gland responds to a variety of stimuli. Of these stimuli, deficiencies and excesses in certain elements contained in the food have received attention. Although the majority of workers have reported that the lack of iodine brings about

an enlargement with hyperplasia of the thyroid gland of the rat,[7] a small number have failed to confirm this observation.[8] The findings in the present study indicated the essential importance of segregation in dietetic experiments in which the final results are dependent on variations in the intake of iodine.

The problem of an unknown etiologic factor affecting investigations on goiter produced experimentally in areas of endemic goiter has been repeatedly raised. Since the production of goiter in rats on the Steenbock rachitogenic diet has recently been demonstrated not only in this endemic zone,[9] but also in a goiter-free district,[7e] such an influence was considered to be precluded from the present study.

The finding of variations in the histologic structure of the thyroid glands of rats in both the normal and the pathologic groups was usual and unavoidable.[10] Such influences as individual susceptibility, transient physiologic demands, unrecognized intercurrent infections, sex, size, season, intake of food and differences in the composition of food (e. g., new grains, inadequate mixing) have some effect in producing these variations. In any biologic test such factors should not be entirely disregarded. In view of the limited knowledge, it seems impossible to estimate just how much of the response to attribute to each agent.

The findings in this study further substantiated the previous observation that the addition of small amounts of iodine counteracted the effect of diets capable of producing hyperplasia of the thyroid gland of the rat.[7h] These results, however, were not in accord with certain recent views expressed in the literature relative to human consumption of iodized salt. The opinions that the increased incidence of toxic goiter in human beings may be directly related to the use of iodine in some cases,[11] and that the close supervision of those to whom iodine is

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7. (*a*) Drennan, A. M.; Malcolm, J., and Cox, G. A.: Brit. J. Exper. Path. **12**:430, 1931; (*b*) Hayden, E. M.; Wenner, W. T., and Rucker, C. W.: Proc. Soc. Exper. Biol. & Med. **21**:546, 1923-1924; (*c*) Krause, W. E., and Monroe, C. F.: J. Biol. Chem. **89**:581, 1930. (*d*) McClendon and Williams.[2a] (*e*) Remington, R. E.: J. Biol. Chem. **97**:CI, 1932. (*f*) Sorour, M. F.: Beitr. z. path. Anat. u. z. allg. Path. **71**:267, 1923. (*g*) Tanabe, H.: ibid. **73**:415, 1925. (*h*) Thompson, J.: J. Nutrition **5**:359, 1932. (*i*) Levine, Harold: J. Biol. Chem. **97**:c, 1932.

8. (*a*) Hellwig, C. A.: Arch. Path. **11**:709, 1931. (*b*) Jackson, C. M., and P'an, M. T.: Endocrinology **16**:146, 1932.

9. Krause and Monroe.[7c] Thompson.[7h]

10. Marine, Lenhart, Kimball and Rogoff.[2b] McCarrison and Madhava.[5c]

11. Bircher, E.: Beitr. z. klin. Chir. **141**:580, 1927. Jones, D. W. C.: Proc. Roy. Soc. Med. **21**:1217, 1928. Ledoux, E.: Rev. de méd. **41**:225, 1924. McClure, R. D.: J. A. M. A. **88**:595, 1927. Maurer, E.: Ztschr. f. Ernähr. **1**:267, 19. Potter, E. B., and Morris, W. R.: Tr. Am. A. Study Goitre, 1932. Raab, W.: Wien. klin. Wchnschr. **44**:309, 1931. Vienna Foreign Letter, J. A. M. A. **96**:1522, 1931. Zimmermann, H.: München. med. Wchnschr. **78**:52, 1931.

being administered as a preventive measure is desirable,[12] lead one to believe that small amounts of iodine may not be entirely harmless. In contrast to the preceding evidence, goiter has been reported to develop in rats maintained on diets containing large amounts of iodine.[13] Whether these findings may be attributed to the iodine per se seems questionable in view of the beneficial effects on the growth of rats reported by Hanzlik and his co-workers,[14] who used comparable amounts of iodine in so-called complete and deficient diets. The lack of deleterious effects in the present study following the daily consumption of the iodine-containing diets by the rats over a period of seven months afforded speculation. These divergent findings may in part be due to the following possible factors: of the human beings affected, a number had definitely or incipiently pathologic changes in their glands prior to the use of iodized salt; the present experiment was of insufficient duration; the tolerance of the rat for iodine is relatively greater than that of man; a disproportion existed between the inorganic or organic constituents of the human intake of food. It must be conceded, however, that the conditions in the animals on the high calcium plus iodine diet were considered to favor the development of a goitrous process. The negative results on this diet may be related to the dosage, the amount used being insufficient to promote the manifestations reported from the exhibition of large doses of iodine to rats, although adequate to inhibit the influence of calcium.

A renewed interest in the relation of calcium to goiter has been taken by a few investigators. Tanabe [7g] and Thompson [7h] recently reported experiments which suggest that the addition of calcium enhances the degree of hyperplasia occurring in rats on low iodine diets. Hellwig,[8a] repeating Tanabe's work, found that calcium added to the drinking water initiated hyperplasia in the rat. Wilms [15] observed that water from goitrous districts lost its activity after precipitation of its calcium by boiling. Although Sorour,[7f] Remington,[7e] Levine [7i] and Drennan, Malcolm and Cox [7a] did not emphasize the fact, their findings showed that hyperplastic changes resulted in animals maintained on high calcium-low iodine diets. In contrast, McCarrison and Madhava [5e] found that the addition of small amounts of lime to mixed diets produced an increase storage of colloid in rats and pigeons. This observation was supported by Kottman's [16] opinion that calcium increased the viscosity of the colloid in the thyroid gland.

12. McCreary, J. B.: Pennsylvania M. J. **34**:189, 1930.

13. Spence, A. W.: Brit. J. Exper. Path. **13**:157, 1932. McCarrison and Madhava.[5e]

14. Hanzlik, P. J.; Talbot, E. P., and Gibson, E. E.: Arch. Int. Med. **42**:579, 1928.

15. Wilms, M.: Deutsche med. Wchnschr. **36**:604, 1910.

16. Kottman, cited by Hellwig.[8a]

Aside from the preceding pathologic evidence, other investigations have indicated that disturbances occur in the calcium metabolism of patients with hyperthyroidism, and that such disturbances occur following the administration of thyroid preparations to man and to animals. These disturbances were evidenced in an excessive elimination of calcium.[17] Aub and his co-workers [17a] were of the opinion that the excessive calcium was derived from the bony depots. That decalcification of the bones has been frequently demonstrated in long-standing cases of hyperthyroidism,[18] and that the addition of thyroid to a borderline rachitogenic diet made the diet definitely rachitogenic [19] favored this view. Some unpublished results have shown that a longer period was required to produce marked rickets in rats when a small amount of iodine was added to a low iodine, rachitogenic diet capable of initiating marked rickets in three weeks. This observation added further support to Aub's suggestion. The metabolic studies of Abelin [20] demonstrated that calcium carbonate lowered the action of thyroxine in rats.

In an attempt to gain an insight into the results obtained in the present study, certain factors relative to the absorption of calcium and iodine were considered. In this connection the acid-base value of diets has been thought of importance.[21] It has been suggested that a preponderance of alkali over acid elements in diets, as well as in the products of digestion, may interfere with the absorption of these elements through increasing the alkalinity of the intestinal contents. In the experimental diets employed in this study, the addition of 3 per cent calcium carbonate necessarily involved a greater relative alkalinity in comparison with the basal diet. Redman, Willimott and Wokes [21c] and McRobert [22] showed that the gastro-intestinal tract of the average adult rat is acid, although McRobert [22] indicated that a small portion of the lower part of the ileum is usually alkaline. This alkalinity could be prevented by adding certain foods to the diet, among which were

17. (*a*) Aub, J. C.; Bauer, W.; Heath, C., and Robes, M.: J. Clin. Investigation **7**:97, 1929. (*b*) Kummer, R. H., cited by Aub, Bauer, Heath and Robes. (*c*) Parhon, M., cited by Aub, Bauer, Heath and Robes. (*d*) Peters, J. P.: Am. J. Surg. **10**:530, 1930. (*e*) Scholz, W.: Ztschr. f. exper. Path. u. Therap. **2**:271, 1905.

18. Aub, Bauer, Heath and Robes.[17a] Dunlap, H. F., and Moore, A. B.: M. Clin. North America **12**:1511, 1929. Plummer, W. A., and Dunlap, H. F.: Proc. Staff Meet. Mayo Clin. **3**:119, 1928.

19. Mellanby, E.: J. Physiol. **57**:ii, 1923.

20. Abelin, I.: Biol. Abstr. **3**:18587, 1929.

21. (*a*) Bauer, W.; Albright, F., and Aub, J. C.: J. Clin. Investigation **7**:75, 1929. (*b*) Farquharson, R. F.; Salter, W.; Tibbetts, D. M., and Aub, J. C.: ibid. **10**:221, 1931. (*c*) Redman, T.; Willimott, S. G., and Wokes, S.: Biochem. J. **21**:589, 1927.

22. McRobert, G. R.: Indian J. M. Research **16**:545, 1928.

tomatoes; this directly applies to the diets employed in this study. That the acid-base value of the diets in this study affected the p_H of the intestine in these experiments was considered doubtful, since the contents from different parts of the tract were examined from time to time, and in no instance did the p_H exceed 6.8. Stewart and Percival [23] stated that the calcium ions remain free as long as the p_H remains below 7. Iodine molecules have been considered more free in an acid medium. Greenbaum and Raiziss [24] showed that while potassium and sodium iodide were almost entirely excreted by the kidney, calcium iodide differed, approximately half appearing in the urine, and the remainder being eliminated with the feces. The preceding observations indicate that the gastro-intestinal tracts of the experimental animals presented conditions favorable and unfavorable for the assimilation of calcium and iodine. In all of the experimental animals the acidity of the contents of the intestine favored the availability of both calcium and iodine. Utilization might have been interfered with by the formation of calcium iodide in diets containing a large amount of calcium. In such a dietary study, the balance between these factors will be involved.

The tentative deductions suggested are as follows: Other factors being constant, the largest amount of iodine would be assimilated from diets low in calcium; a relatively greater iodine deficiency would be likely to occur in animals receiving a low iodine diet containing large amounts of calcium; an increased amount of iodine would be necessary to meet the body's requirement if there was an associated high consumption of calcium.

The importance of the inorganic composition of diets in relation to organic function is becoming increasingly recognized. When certain mineral elements are unbalanced, characteristic pathologic abnormalities develop.[25] On this basis, the existence of a balance between iodine and calcium might be considered.

An explanation of the association of iodine and calcium with changes in the thyroid gland involved the hypothesis that there must be a definite equilibrium of these two elements within the body to insure normal function of the thyroid gland. Since a considerable range of individual variation of the elements in a mineral balance may occur prior to the appearance of signs or symptoms referable to a disturbance, a certain degree of fluctuation must be recognized in relation to the iodine-calcium balance. Furthermore, if a disproportion exists in an

23. Stewart, C. P., and Percival, G. H.: Physiol. Rev. **8**:283, 1928.

24. Greenbaum, F. R., and Raiziss, G. W.: J. Pharmacol. & Exper. Therap. **30**:407, 1927.

25. McCollum, E. V., and Simmonds, N.: The Newer Knowledge of Nutrition, ed. 4, New York, The Macmillan Company, 1929.

elemental balance, an attempt is made by the body to reestablish an equilibrium by mobilizing any available reserves. From this it follows that a disturbance of the balance between iodine and calcium beyond certain limits is associated with the goitrous state. The results obtained in this and in other studies previously noted, in which disturbances in the calcium metabolism were found in conjunction with abnormalities of the thyroid gland, have lent credence to this view.

In applying this theory to the present results, it will be recalled that if the available iodine is reduced by feeding a low iodine diet, the activity of the thyroid gland is increased in an attempt to supply the necessary requirement of synthetic iodine compounds Microscopically, this is evidenced by a decrease in stainable colloid, hypertrophy and hyperplasia of the cellular elements. The amount of change has been related more or less closely to the duration and the degree of the deficiency. If, in addition, a balance between iodine and calcium has to be maintained, an associated increase in calcium exerts a further stimulating effect on an already overworking gland. The experimental findings in animals on the high calcium-low iodine diet supported this assumption. A deficient intake of both elements induced less marked changes in the thyroid glands of animals on the low calcium-low iodine diet. In this instance, although a response was to be expected owing to the deficiency of iodine per se, the factor of equilibrium exerted little influence. In relation to the group on low calcium plus iodine diet, it must be admitted that the results were inconclusive, since the animals were carried on this diet for only two months. In this group the balance may have been disturbed or it may have been normal. If it was abnormal, the calcium reserves sufficed to maintain equilibrium throughout the experimental period. On the other hand, the fluctuation in iodine may have been within the range of the balance. The finding of nonhyperplastic glands in animals on the high calcium plus iodine diet was explicable on this hypothesis. In this diet, although the quantity of both constituents doubtless exceeded the normal requirements, the balance was maintained at a higher level.

SUMMARY

The thyroid glands of 254 rats have been studied under experimental conditions. The gross manifestations were frequently misleading criteria on which to base an opinion regarding the histologic state of the thyroid gland.

In animals on diets deficient in iodine there was a gross enlargement of the gland associated with hypertrophy and hyperplasia. In some cases this condition had subsequently reverted to atrophy. The addition of calcium carbonate to diets similarly deficient in iodine resulted

in a greater and more rapid increase in the size of the gland, as well as in a more marked acinar hyperplasia. The addition of a small amount of iodine to the diets prevented the development of hyperplasia.

The experimental evidence was considered indicative of an intimate interrelationship between iodine and calcium in the production of goiter. On this basis, the theories of the incitation of goiter by deficiency of iodine and an excess of calcium appeared to be correlated.

EXPERIMENTAL PATHOLOGY OF THE LIVER

XII. EFFECTS OF FEEDING DESICCATED THYROID GLAND ON RESTORATION OF THE LIVER

GEORGE M. HIGGINS, PH.D.
Associate Professor of Experimental Biology, the Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota
ROCHESTER, MINN.

The ability of the liver to restore a normal amount of parenchyma following loss sustained either by partial surgical removal or by pathologic changes is well known, but the physiologic factors which induce such rapid recovery are as yet imperfectly understood. Recent observations on the dog, white rat and chicken seem to indicate that restoration may be correlated with the volume of blood entering the hepatic remnant. When a large portion of hepatic parenchyma is removed, the available hepatic capillary bed for the portal blood is correspondingly reduced, whereas the volume of blood in the portal vein remains essentially the same.

Data on the restoration of the livers of rats maintained on various diets give evidence of considerable difference in the amount of parenchyma restored. These data, too, may be correlated, not so much with the factors related to diet, but with the volume of blood entering the liver through the portal vein. This report is based on the results obtained in a study of the restoration of the liver in rats maintained on a standard ration to which had been added small portions of desiccated thyroid gland.

EXPERIMENTAL METHODS

Attempts were first made to develop a condition of hyperthyroidism by the subcutaneous injection of thyroxine. Normal, healthy rats, which were on a standard ration, and the daily weights of which were increasing, were given doses of 0.5 mg. of thyroxine daily. Loss of weight and other indications of increased metabolic activity were apparent in a few days, but immediately after the surgical removal of 75 per cent of the liver each of these rats died. In a second series of rats hepatectomy was performed before marked effects of thyroxine were induced; again each of the rats died immediately after partial removal of the liver. Accordingly, thyroxine was discontinued, and 1 per cent by weight of desiccated thyroid gland was added to the normal ration to induce characteristic changes. The data on the daily consumption of food indicated that each rat consumed about 150 mg. of the dried gland each day. Eighteen rats were then isolated for two weeks, fed the standard ration and weighed every two days. During this period the

From the Institute of Experimental Medicine, the Mayo Clinic.

rats increased in weight from an average of 169.3 to 195.6 Gm. The thyroid ration was then added to the diet, and a decrease in the weight of the body was soon observed. After a week of this dietary regimen, the usual hepatic component was removed from each rat. Here again, as when thyroxine had been given, the rats died immediately after operation. Thus these preliminary experiments proved that rats in which hyperthyroidism had been induced either by the ingestion of thyroxine or by the administration of desiccated thyroid gland could not withstand the loss of 70 per cent of the liver.

In order to secure data concerning restoration of the liver when the rat was subjected to the effects of desiccated thyroid gland, the liver was partially removed before feeding with the gland was commenced. Fifty-four rats, aged from 6 to 8 months, were isolated, maintained on the standard ration and subjected to partial hepatectomy. Immediately afterward, the rats were placed on the standard ration to which was added the 1 per cent desiccated thyroid gland; they continued to eat this during the period of observation. Groups of five rats each were killed by exsanguination after three, seven, fourteen, twenty-one and twenty-eight days, respectively; the weight of the restored parenchyma was determined, and the ratio of the weight of the liver to the weight of the body was computed for each rat. As a basis of comparison, a series of rats, comparable in every way with those operated on, were placed on an identical thyroid ration and were killed at corresponding intervals, in order to secure data on the weight of the liver and on the ratio of the weight of the liver to the weight of the body of the rat not operated on during the period of experimental observation.

To establish satisfactory control data on the weights of the livers and the weights of the rats, twenty-five rats ranging in weight from 128 to 214 Gm., with an average body weight of 156.04 ± 2.684 Gm., were killed. The average weight of the livers of this control group was 6.576±0.3890 Gm., and the average ratio of the weight of the liver to the weight of the body was 0.0421. From a knowledge of averages, standard deviations and correlation coefficients, a linear equation was computed, which would describe one variable in terms of the other. If x was the weight of body and y the weight of liver, then y was computed to be $0.0505\ x - 1.302 \pm \frac{0.3800}{\sqrt{n-1}}$ Gm. With this equation, therefore, the preoperative weight of the liver was computed on the basis of the preoperative weight of the body for each rat experimented on.

EXPERIMENTAL OBSERVATIONS

All data for this study have been condensed (table 1, charts 1 and 2). All the rats lost weight because of the onset of hyperthyroidism. Rats killed had lost weight as follows: at the end of the third day, 9.5 per cent of their original weight; at the end of the seventh day, 18.5 per cent; on the fourteenth day, 15.1 per cent; on the twenty-first day, 18.4 per cent, and on the twenty-eighth day, 14.6 per cent. Other features such as rough coat and hypersensitiveness were noted; diarrhea was not observed. Since all the rats lost weight, it seemed desirable to compute the amount of liver restored after partial removal, not only in grams, but in percentages related to the preoperative weight and the attained weight of the body.

The weights of the livers recorded at the end of the third day after partial removal indicated that the restorative process in the thyroid-fed rats was well under way, although it was no greater in these rats than in rats fed normal rations (chart 1). At the end of the first week, however, the livers of the thyroid-fed rats manifested some increase in restoration over those serving as controls. On the basis of the original, or preoperative, weight of the body, the thyroid-fed rat had a hepatic parenchyma of 2.8 Gm. per hundred grams of body weight as against

TABLE 1.—*Summary of Data on Restoration of the Livers of Rats Given Desiccated Thyroid Gland with the Ration*

Group	Weight of Animal Prior to Partial Hepatectomy, Gm.	Weight of Liver* Prior to Partial Hepatectomy, Gm.	Liver Removed at Operation, Gm.	Liver Remaining After Partial Hepatectomy, Gm.	Weight of Body When Rat Was Killed, Gm.	Weight of Liver When Rat Was Killed, Gm.	Actual Increase of Liver During Restoration, Gm.	Weight of Liver During Restoration, per Cent of Body Weight: Preoperative	Weight of Liver During Restoration, per Cent of Body Weight: Postoperative
Rats operated on (54).....	168.3± 2.41	7.197± 0.052	4.09± 0.080	3.107± 0.095					
72 hours postoperatively	165.0± 10.80	7.030± 0.190	4.26± 0.995	2.770± 0.439	149.2± 10.78	4.12± 0.233	1.350± 0.497	0.025	0.027
7 days postoperatively	157.9± 4.52	6.671± 0.190	4.14± 0.126	2.531± 0.228	128.6± 6.11	4.40± 0.067	1.869± 0.237	0.028	0.034
14 days postoperatively	155.6± 3.55	6.555± 0.190	3.32± 0.148	3.235± 0.241	152.0± 4.65	6.78± 0.269	3.545± 0.361	0.043	0.051
21 days postoperatively	181.4± 9.67	7.858± 0.190	4.36± 0.273	3.498± 0.332	148.0± 11.38	8.10± 0.849	4.602± 0.912	0.045	0.054
28 days postoperatively	156.4± 2.93	6.596± 0.190	3.90± 0.091	2.696± 0.210	133.6± 3.17	7.52± 0.219	4.824± 0.303	0.048	0.056

* Regression formula: Weight of liver = 0.0505 (weight of body) − 1.302 ± $\frac{0.3800}{\sqrt{n-1}}$ Gm.

2.7 Gm. in the control series. From this time on, the discrepancy in the two curves representing the extent of hepatic restoration in the two series of rats was all the more marked (chart 1). The average weight of the livers of the thyroid-fed rats killed after fourteen days was 4.3 Gm. as against 3.2 Gm. recorded as the average weight when rats were fed the ration without the desiccated gland. From the fourteenth to the twenty-eighth day, the curves are roughly parallel, and at the end of the fourth week of restoration the average weight of the livers was 4.9 Gm. for the rats fed on thyroid gland in contrast to 4 Gm. for the control rats. The impetus to more rapid restoration when the rats were

fed the thyroid ration occurred some time during the second week, after which the rate of recovery was more or less constant.

When the percentage of the amount of parenchyma restored in relation to the weight of the rat was considered, a similar divergence between the livers of rats on the normal ration and the livers of the rats on the thyroid ration was apparent. In chart 2 the ratio of the amount of parenchyma to the preoperative weight and that to the attained weight of the body are plotted. The changes in the liver were considered on the basis of the preoperative weight of the body, as the decrease in the weight of the rats was slightly more in those fed

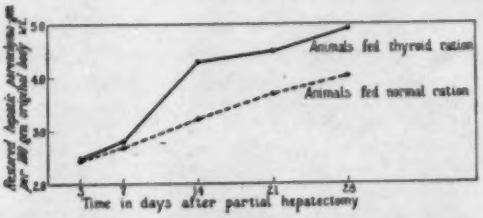

Chart 1.—Comparison of the average percentage weight of the livers of partially hepatectomized rats fed a thyroid ration with the average percentage weight of the livers of partially hepatectomized rats fed a normal ration.

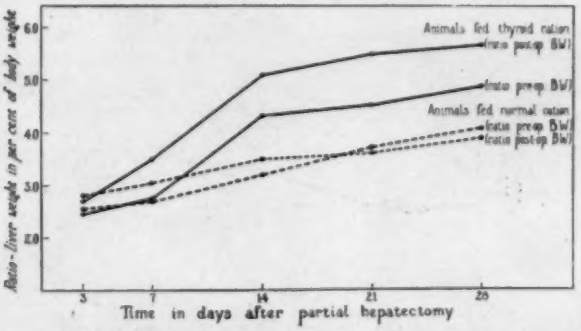

Chart 2. —Ratios of the weight of the liver to the weight of the body during restoration.

the desiccated thyroid gland. The curve of these ratios (chart 2) from determinations made at three, seven, fourteen, twenty-one and twenty-eight days after partial hepatectomy shows clearly that the average increase in weight of the livers was considerably greater for each unit of body weight when the rats were fed the desiccated gland. This is true whether these percentages were computed on the basis of the preoperative weights of the rats or on the basis of their weights at the time they were killed. A real discrepancy between the curves was not apparent until the fourteenth day. On the third day, the percentages

in the two groups were more or less alike, and at the end of the week the percentages of the weights of the livers being restored computed on the basis of the average weight of the animals just prior to operation were essentially alike in the rats fed on thyroid gland and in the normal control rats. The gain in the average percentage of weight of liver in relation to weight of body attained at the fourteenth day by the rats fed on thyroid gland was maintained to the end of the experiment, when there was an average ratio of 0.048 in contrast to 0.041 among the control animals operated on. Accordingly, it seemed that the maintenance of partially hepatectomized rats on a thyroid diet increased the extent of restoration of the liver.

TABLE 2.—*Changes in Average Weight of Livers of Rats not Operated on Maintained on Thyroid Ration*

Group	Number	Weight of Body, Gm.	Estimated* Weight of Liver, Gm.	Weight of Liver When Rat Was Killed	Change in Weight of Liver, Gm.	Percentage of Weight of Liver in Relation to Original Weight of Body
All animals	20	153.8 ± 2.200	6.465 ± 0.0850	.....	.....	0.0420
7 days.....	5	142 ± 6.101	5.869 ± 0.1900	5.760 ± 0.1780	−0.109 ± 0.2603	0.0405
14 days.....	5	150 ± 5.127	6.707 ± 0.1900	7.070 ± 0.5598	+0.363 ± 0.5911	0.0445
21 days.....	5	157 ± 5.102	6.626 ± 0.1900	7.760 ± 0.2171	+1.134 ± 0.2884	0.0494
28 days.....	5	157 ± 5.352	6.626 ± 0.1900	7.880 ± 0.1545	+1.254 ± 0.2449	0.0502

* Regression formula: Weight of liver = 0.0505 (weight of body) − 1.302 ± $\frac{0.3800}{\sqrt{n-1}}$ Gm.

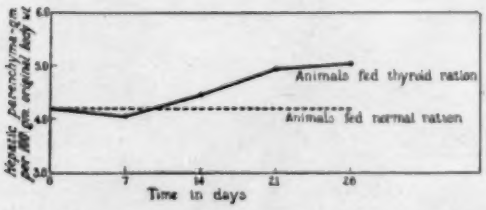

Chart 3.—Comparison of the changes in the average percentage weight of the livers of rats not operated on but fed thyroid ration with the changes in the average percentage weight of the livers of rats not operated on which were fed a normal ration.

Normal rats not operated on were also studied to determine the effect such a diet might have on the weight of the liver and the ratio of the weight of liver to the weight of body. Twenty rats, known to be healthy and of comparable strain, were isolated and fed the normal ration plus the thyroid ration in amounts similar to those fed the hepatectomized rats. The average weight of these rats was 153.8 ± 2.2 Gm. and, by means of the regression equation, the average weight of the livers was estimated to be 6.46 ± 0.09 Gm. The average per-

centage of the weight of the liver in relation to the weight of the body was 0.042. Five rats were killed each week for four weeks, and the changes in the average weight of the animals and the average weight of the livers from the estimated average weight before thyroid gland was fed were computed (table 2).

The rats not operated on lost weight as did the hepatectomized rats. After seven days of feeding with thyroid gland, an average loss of 8 Gm. was recorded; the rats killed at the end of the second week had lost 4 Gm., and those killed at the end of the fourth week had lost 2 Gm. The changes in the amount of hepatic parenchyma of rats killed after one, two, three and four weeks of being fed the thyroid ration are condensed (table 2, chart 3). The average weight of the livers of rats killed at the end of the first week was 0.109 Gm. less than that estimated before the rats were placed on the thyroid ration. Increases in the weight of the hepatic parenchyma of rats fed the desiccated thyroid ration were not marked until in the second week. No immediate or initial effects were induced. The same reaction, it will be recalled, occurred after partial hepatectomy. It was not until the fourteenth day after operation that the average weight of the livers of rats fed thyroid gland considerably exceeded that of rats fed the standard ration and operated on. The average weight of the livers of rats fed desiccated thyroid gland and not operated on increased 0.363 ± 0.59 Gm., and this rate of increase continued, so that after four weeks of the diet, the increase was greater by 1.254 ± 0.25 Gm. when the rats were fed the thyroid ration.

SUMMARY

The addition of 1 per cent, by weight, of desiccated thyroid gland to a standard ration increased the extent of the restoration of the liver following partial surgical removal. Similarly, the livers of rats not operated on, and fed the thyroid ration, increased in size after the second week, and by the fourth week were greater by 20 per cent than their estimated preexperimental weights.

Laboratory Methods and Technical Notes

AN INEXPENSIVE APPARATUS FOR ROUTINE PARAFFIN EMBEDDING IN VACUO

With Notes on the Technic of Dehydration, Clearing and Paraffin Infiltration of Tissues

R. D. Lillie, M.D., Washington, D. C.
Surgeon United States Public Health Service

While the use of a vacuum in facilitating the infiltration of tissues with paraffin has been known at least since 1884 (Lee [1]), the procedure appears to have been little employed. Its advantages in economy of time, reduction of the period of immersion of tissues in melted paraffin and superior infiltration of the tissues containing internal cavities were pointed out by Lee.

Three or four years ago I employed an extemporaneously arranged vacuum to facilitate the infiltration of pulmonary tissues with paraffin. The results were so favorable that an inexpensive apparatus for the routine use of a vacuum in paraffin embedding was devised and has been in regular use for about three years.

DESCRIPTION OF APPARATUS

The essential part of such an apparatus is a chamber in which a vacuum may be maintained at the temperature of melted paraffin. My associates and I have found satisfactory a 6 or 8 quart aluminum pressure cooker such as is sold for kitchen use for $7 or $8. The type having hinged lugs with winged nuts to hold the lid on is more satisfactory than the type with a compression collar.

Such pressure cookers have on the lid a safety valve, an aneroid pressure gage and a release valve. The safety valve and the pressure gage are unscrewed and removed and are replaced by screw plugs. The release valve is retained and is used for releasing the vacuum.

A pipe line to a vacuum pump must be supplied. For this purpose a hole is tapped through the side of the pressure cooker near the top, a piece of threaded pipe is passed through the hole and nuts are applied inside and outside the wall of the cooker and screwed tightly against the wall from both sides. To the outer end of the piece of iron or brass pipe a length of ½ inch (1.2 cm.) lead pipe is attached which leads to a three-way stopcock. One of the other two openings of this stopcock leads to the upper end of a piece of heavy glass tubing 40 inches (101 cm.) long which is attached vertically to the wall of the laboratory and the lower end of which dips into a bottle of mercury. A yardstick or meter-stick

From the National Institute of Health.

1. Lee, Arthur Bolles: The Microtomist's Vade-Mecum, ed. 7, Philadelphia, P. Blakiston's Son & Co., 1921, p. 80.

fastened to the wall beside the glass tube completes the vacuum gage. The third opening of the stopcock is attached to another length of lead pipe which leads to the vacuum pump. An ordinary 250 cc. vacuum flask of heavy glass is inserted into this line near the pump to serve as a trap for water or oil from the pump.

This vacuum chamber may be placed on its side on a small sheet metal support inside an ordinary paraffin oven or a 60 degree incubator. The pipe line to the three-way stopcock leads out through one of the holes in the side or the top of the incubator. A double shelf, furnishing two shelves for small beakers or bottles, may be inserted in the vacuum chamber.

In case a paraffin oven or a 60 degree incubator is not available, the vacuum chamber may be placed upright on a sheet metal collar in a hotel size soup stock pot which serves as a water bath. A thermostat element such as is used for gas-

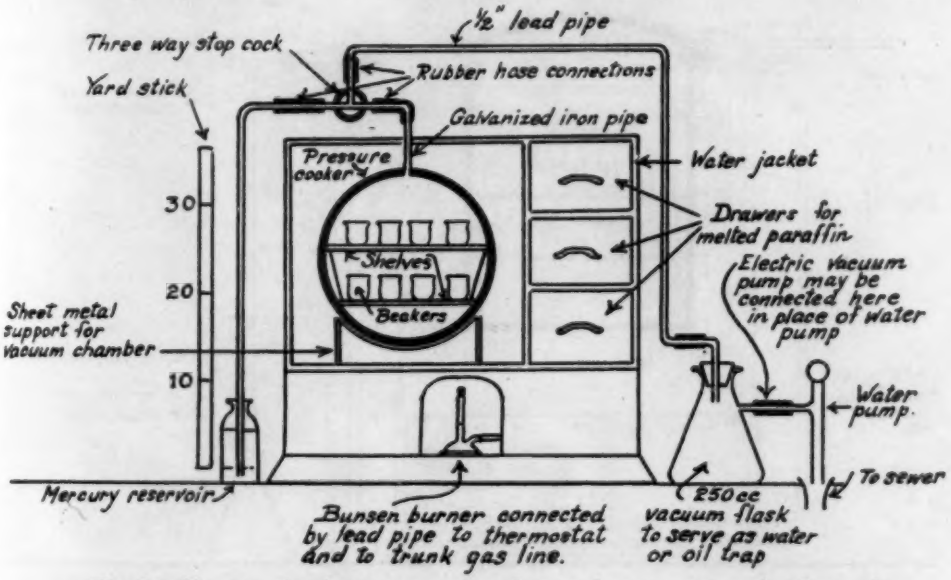

Fig. 1.—Diagram showing a pressure cooker used as a vacuum chamber and installed in an ordinary paraffin oven.

heated water baths may be inserted through a hole in the sheet metal collar beside the vacuum chamber, and the temperature may be satisfactorily regulated by this means. The trays ordinarily supplied with pressure cookers may be used as shelves and the bottom used for the stock supply of melted paraffin.

The accompanying diagrams (fig. 1 and 2) illustrate fully the two types of installation.

A pump capable of reducing the pressure inside the chamber to from 25 to 50 mm. of mercury is desirable, though pressures as high as 125 mm. may be quite satisfactory.

TECHNIC OF EMBEDDING IN PARAFFIN

The following technic permits routine embedding in from three to five hours after cutting blocks of fixed material:

Blocks from 1 to 3 mm. thick are immersed in four successive baths of acetone of from thirty to forty minutes' duration. For the last change, fresh acetone

of U. S. P. grade, costing about $1.50 per gallon, is used. For the third change we employ the acetone which has been used once for the last change, which is then used similarly for the first two changes. The acetone used for the first change is discarded or put aside for redistillation. The final acetone bath is followed by thirty minutes in benzene or from thirty to sixty minutes in cleaner's gasoline. After this, the specimens are placed in melted paraffin in the vacuum chamber, the chamber is closed and the pump turned on until the mercury rises 28 or 29 inches (71 to 73 cm.) in the gage. The three-way stopcock is then turned so that the

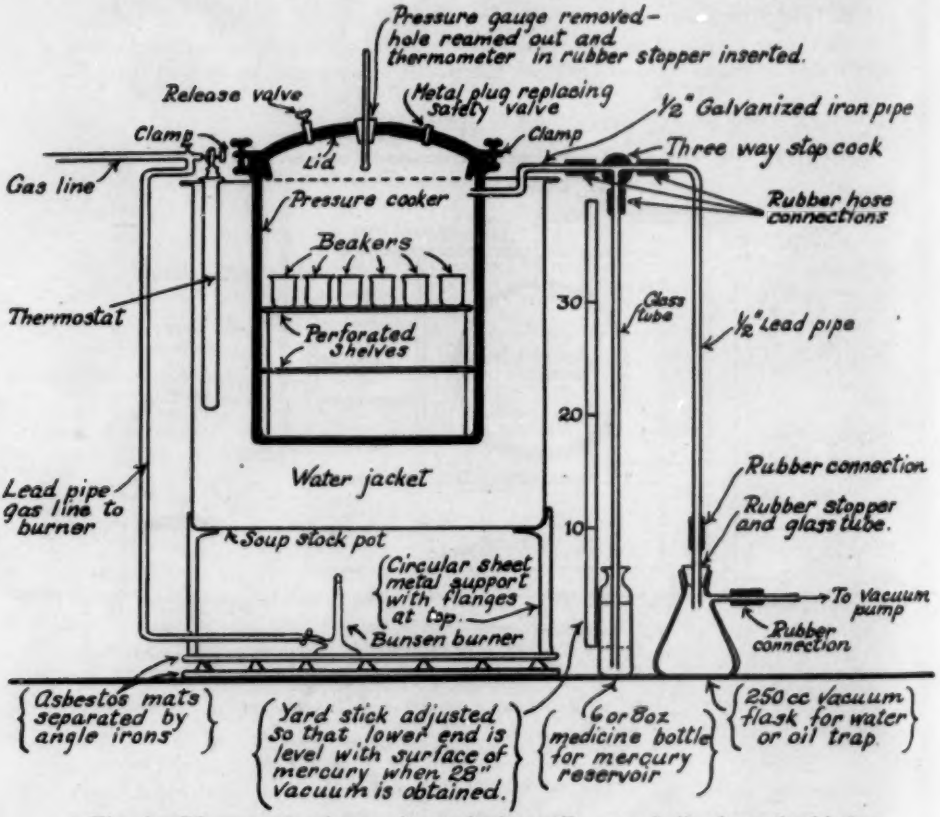

Fig. 2.—Diagram showing an improvised paraffin oven built about the kitchen type of pressure cooker and used as a vacuum chamber.

chamber remains connected with the gage but not with the pump line. Ten minutes later the release valve is opened and the vacuum released. When the objects are difficult to embed, the exhaustion of the chamber may be repeated. The chamber is then opened, and the objects are embedded as usual. Individual wire gauze covers for the specimen bottles or beakers should be provided, as the paraffin sometimes boils over and specimens may thus be lost. A square of fine-meshed copper gauze, an inch wider than the top of the bottle or beaker, folded down onto the sides of the container is a satisfactory cover. It may be cleaned by burning off the paraffin.

A volatile paraffin solvent, such as xylene, benzene, chloroform or gasoline, should be used, as nonvolatile solvents remain in the paraffin and impair its consistency. Cleaner's gasoline is the most generally satisfactory, as it hardens tissues less than any of the others. The cleaner's grade should be insisted on, as fuel gasolines commonly contain some nonvolatile oil.

This technic causes remarkably little shrinkage. The infiltration of air-containing tissues as well as of ordinary parenchymatous and fleshy tissues is excellent. Shrinkage of the tissues within the paraffin blocks after a period of storage is never seen.

For tissues containing large amounts of fat, which are notoriously difficult to section after being embedded in paraffin, we find that interposing about four successive thirty minute baths in benzene between the dehydration with acetone and the infiltration with paraffin greatly improves the consistency.

Shrinkage of the pyramidal cells in formaldehyde-fixed blocks of cerebral cortex may be avoided by incubating the blocks for twenty-four hours at 37 C. in 2.5 per cent potassium dichromate, transferring them to 50 per cent alcohol for one-half day and to 80 per cent alcohol for another half day or longer, as may be convenient, and then dehydrating, clearing and embedding as described.

Very tough tissues which are difficult to cut both in the gross and after embedding may be improved in consistency by passing them from the final acetone bath into cedar oil for over night or longer. It is then necessary to remove the cedar oil before infiltration with paraffin by immersing the blocks in two successive thirty minute baths of gasoline or benzene. Used cedar oil may be freed from acetone by putting it in a beaker in the vacuum chamber at from 57 to 58 C. and leaving it for twenty minutes in vacuo; it is then as good as fresh cedar oil for clearing.

General Review

HYPERPARATHYROIDISM (RECKLINGHAUSEN'S DISEASE OF BONE)

HENRY L. JAFFE, M.D.
NEW YORK

(Concluded from page 112)

CLINICAL FEATURES

The indications for diagnosis, on the basis of symptomatology, vary with each case.

Sex and Age.—No sex factor is indicated for this disease; the incidence of reported authentic cases seems to favor the female, but if this is so, the finding is purely accidental. Most patients seem to fall in the middle adult group (from 30 to 50 years). Cases of hyperparathyroidism have, however, been reported in children and in adults over 50 years of age.

Pain.—Study of the histories of many proved cases brings out strikingly the importance of pain as a dominant clinical feature. The pain is generally referred to the bones and joints of the lower extremities and to the spine; it is exaggerated by physical activity, although it may be present in repose. In the evolutionary stages of the disease, especially before the development of deformities or fractures, the patient may go the rounds of physicians and clinics seeking relief for what is suspected to be rheumatic pain. As the disease progresses, the pain may become so severe that the patient winces with pressure on, or compression of, the bones. Snapper's [110] patient suffered so severely from pain that he could not bear the weight of the ordinary bed sheets. Quick and Hunsberger,[111] in giving the clinical history of their patient who suffered extreme deformity of almost the entire skeleton, noted the absence of pain; however, they mentioned pain as a distressing symptom in this patient during the earlier evolutionary stages of the disease.

Muscular Weakness and Hypotonia.—Muscular weakness and lassitude are early manifestations of the disease and are frequently associated with the pain. Difficulty in coordinating muscular movements may also be experienced. Hypotonia to a marked degree may eventually

From the Laboratory Division, Hospital for Joint Diseases.

110. Snapper, I.: Arch. Int. Med. **46**:506, 1930.

111. Quick, A. J., and Hunsberger, A.: J. A. M. A. **96**:745, 1931.

assert itself. Diminished electrical irritability of muscle and nerves occurs, possibly twice the amount of current normally required being needed to produce normal reactions. The relation of electrolytes to the contractility of tissues has long been established. After removal of the parathyroids, the low serum calcium and high serum phosphorus are associated with increased electrical excitability, hypertonia and tetany. In hyperparathyroidism, on the other hand, the increased serum calcium and decreased serum phosphorus are associated with decreased electrical excitability, with hypotonia and with muscular weakness. Hypercalcemia, produced experimentally by the injection of calcium salts, likewise results in hypotonia with a simultaneous decrease of the serum phosphorus. On the other hand, hyperphosphatemia, following the injection of phosphate, results in phosphate tetany, the serum calcium being simultaneously lowered.

Nausea, Vomiting and Constipation.—Nausea and vomiting, sometimes with severe abdominal pain, may accompany the other symptoms, especially in younger patients. When Quick and Hunsberger's [111] patient was about 22 years of age, he complained of persistent nausea. Boyd, Milgram and Stearns [112] reported the case of a man, aged 21, who had periodic attacks of severe abdominal pain and vomiting lasting for about three days and recurring about every three weeks for a year. Pemberton and Geddie's [113] patient, a girl, aged 14, complained chiefly of vomiting, pallor and loss of weight; she had recurrent spells of vomiting (at about two week intervals, lasting from one to five days). The attacks seemed to appear without any direct cause. Ask-Upmark [114] recorded that his patient, who died before operation, had vomited daily for two weeks before admission to the clinic. I am led to interpret such spells of nausea and vomiting as evidences of acute intoxication attributable to acute hyperparathyroidism. It is interesting, by analogy, that in experimental hyperparathyroidism the younger animals are more susceptible to parathyroid extract-Collip than the older ones. Young dogs on a normal diet, with relatively small doses of parathyroid extract, will readily evidence acute intoxication should precautions as to the dosage be relaxed.

Another relevant symptom is the occurrence of constipation; the majority of patients suffer severely from it for a great length of time.

Polydipsia, Polyuria and Urolithiasis.—Increased thirst is common, and is conditioned by the increased excretion of calcium and phosphorus through the kidneys. Since large quantities of fluid are simultaneously excreted with these salts, the thirst, in compensation, becomes pro-

112. Boyd, J. D.; Milgram, J. E., and Stearns, G.: J. A. M. A. **93**:684, 1929.
113. Pemberton, J. deJ., and Geddie, K. B.: Ann. Surg. **92**:202, 1930
114. Ask-Upmark, E.: Acta med. Scandinav. **74**:284, 1930.

nounced. Nocturia may be a distressing feature of the polyuria. Urination may be painful; some patients pass gravel. Renal stones are to be observed, roentgenologically or at autopsy, in as many as one third of the cases of Recklinghausen's disease. In experimental hyperparathyroidism, renal calculi have not appeared, although metastatic calcification of the kidneys is a common feature in acute hyperparathyroidism.

Other Manifestations of the Disease.—These vary with the individual case. Loss of appetite and loss of weight are nearly always present and may become pronounced; the patient is sometimes reduced to such a state of emaciation as to appear utterly wasted. Obvious skeletal deformities may be present; the thoracic cage is often greatly deformed because of the kyphosis and kyphoscoliosis; the extremities may be shortened, secondary to fractures and their resultant deformities. Reduction in height is the natural consequence.

When the disease appears in children, roentgenologic examination of the skeleton may disclose signs strongly suggesting late rickets rather than Recklinghausen's disease. Because of this, roentgenologists have erroneously reported cases of Recklinghausen's disease in children as showing rachitic complication. Duken's [115] case of Recklinghausen's disease in a girl aged 14 presented roentgenologic appearances considered typical of late rickets: a rachitic rosary, widening of the metaphyses and generalized porosis. Cessation of growth had occurred at the age of 12.

Stunting has been observed in other cases of Recklinghausen's disease, when the pathologic processes were very active before full physiologic growth had been attained. Likewise, in young dogs, experimental chronic hyperparathyroidism has led to stunted growth.[30a] Furthermore, Bodansky, Blair and I [42] showed that in hyperparathyroidism in young, growing guinea-pigs such sites as the costochondral junctions and the metaphyses of long tubular bones were most predisposed to changes. The last-mentioned fact explains why in children the lesions of hyperparathyroidism occurring at the costochondral junctions and at the metaphyses should be suspected roentgenologically as being of the nature of rickets.

DIAGNOSTIC AIDS

Serum Calcium and Phosphorus.—Determination of the serum calcium and serum phosphorus is a prime requisite for diagnosis. However, too much reliance should not be placed on any one procedure for aid in determining the presence of hyperparathyroidism. Certainly, the high serum calcium values that may be observed occasionally in

115. Duken, J.: Ztschr. f. Kinderh. **46**:114, 1928.

multiple myeloma or with metastatic carcinoma of bone would be misleading if considered alone in framing a diagnosis. Methods for the determination of serum calcium and phosphorus, as standardized within recent years, have given reliable figures for normal values as well as for values in pathologic conditions. Most serum calcium values for normal adults are between 10 and 11 mg. per hundred cubic centimeters, with relatively few values outside of that range. The serum phosphorus in normal adults may be stated to be about 3 mg. per hundred cubic centimeters.

In clinical hyperparathyroidism, varying degrees of hypercalcemia and hypophosphatemia have been observed. Serum calcium values as high as 23.6 mg. and serum phosphorus values as low as 1.1 mg. per hundred cubic centimeters have been reported. On the other hand, in some cases the serum calcium value may not be consistently high. Wilder [116] reported a case in which most values were within normal range; the higher values (among which 13.2 mg. was the highest) were observed during the period of a diet high in vitamin D and ultraviolet irradiation. The serum calcium values obtained for any patient may fluctuate considerably over a long period.

However, an elevated level of the serum calcium and a depressed level of the serum phosphorus may not necessarily be present, as in a more recent case which Wilder and his associates [117] described. Their patient, a woman of 48 years, had changes in the bones which roentgenographically suggested Recklinghausen's disease, but because the serum calcium and phosphorus values were within normal limits a diagnosis of hyperparathyroidism was not made. At a subsequent examination, nineteen months later, additional roentgenograms showed further progress of the disease, but the values of serum calcium on successive days were 11.5, 11, 10.6 and 11 mg. per hundred cubic centimeters; those of phosphorus were 2.9, 3, 2.7 and 2.3 mg. Since a definite negative balance for calcium was present, it was decided to explore the neck, and a parathyroid adenoma was removed. Bodansky and I [81b] have shown that even hypocalcemia may develop in young dogs suffering from chronic hyperparathyroidism if they are maintained on a diet low in calcium; this hypocalcemia may be associated with tetany.

The existence of a nephritic complication associated with uremia may still further confuse the evaluation of the estimations of serum calcium and serum phosphorus in Recklinghausen's disease. It is well known that the serum phosphorus level is elevated and the serum calcium level is depressed to a very low figure in uremia. When uremia compli-

116. Wilder, R. M.: Endocrinology **13**:231, 1929.

117. Wilder, R. M.; Camp, J. D.; Robertson, H. E., and Adams, M.: Proc. Staff Meet., Mayo Clin. **7**:597, 1932.

cates Recklinghausen's disease—and it may, because of the great frequency of urolithiasis and associated renal infection—the urea nitrogen level becomes greatly elevated as does that of the serum phosphorus, and the serum calcium (which in the absence of the uremia may have been increased) is decreased and reaches normal or subnormal levels.

It is surprising that the ingestion of large quantities of calcium by patients with clinical hyperparathyroidism has little effect on the serum calcium and phosphorus. Thus, the danger of hypercalcemia and hyperphosphatemia during short periods of excessive ingestion of calcium, seems not to prevail. Bauer, Albright and Aub [118] found that during one period when their patient received 9.14 Gm. of calcium and the balance was + 5.02 Gm., the serum calcium was 14 mg. per hundred cubic centimeters and the serum phosphorus 1.7 mg.; during a period with an intake of 0.29 Gm. of calcium and a balance of — 0.95 Gm., the serum calcium was 13.7 mg. and the phosphorus 1.9 mg.

Mineral Metabolism.—Study of the calcium and phosphorus balances constitutes a most important diagnostic chemical procedure to be followed in this disease. A complete study of mineral balance requires so much careful attention to numerous details that in most institutions it is difficult, if not impossible, to carry out such a procedure. Directions for carrying on such studies may be found in the recent papers of Bauer, Albright and Aub,,[119] Bassett, Elden and McCann [120] and Salter, Fulton and Angier.[121] Of the two excretions, measurement of the calcium is by far the more important, as excessive excretion of calcium in the urine is regularly found in active cases. Normally, the urinary excretion of calcium is relatively small and is not materially increased by a high calcium intake. Even intravenous administration of calcium may have little influence on urinary excretion. Thus, in normal persons the great differences in output, resulting from variation in calcium intake, occur chiefly in the stool. As Hannon, Shorr, McClellan and DuBois [28] pointed out, in normal persons from 70 to 90 per cent of the calcium is excreted in the feces and from 10 to 30 per cent in the urine; in those with hyperparathyroidism from 10 to 30 per cent is excreted in the feces and from 70 to 90 per cent in the urine.

In the studies of calcium balance, it seems preferable, as Bauer, Albright and Aub [119] pointed out, to compare the excretion of calcium in normal persons on a diet low in calcium (standardized as to the

118. Bauer, W.; Albright, F., and Aub, J. C.: J. Clin. Investigation **8**:229, 1930.

119. Bauer, W.; Albright, F., and Aub, J. C.: J. Clin. Investigation **7**:75, 1929.

120. Bassett, S. H.; Elden, C. A., and McCann, W. S.: J. Nutrition **4**:235, 1931.

121. Salter, W. T.; Fulton, C., and Angier, F.: J. Nutrition **4**:1, 1931.

ingredients of the diet and its acid-base equivalents). Thus, many variables which influence calcium absorption are avoided; even such factors as age, sex and nitrogen balance have to be considered before accurate comparisons can be made. Two of the three patients studied by Bulger, Dixon and Barr [122] had excessive fecal excretion of calcium, while all three showed excessive urinary excretion of calcium. The patient of Hannon, Shorr, McClellan and DuBois was in negative calcium balance on an intake of 0.5 Gm. a day; 0.7 Gm. daily was necessary to maintain him in equilibrium. A low fecal excretion of calcium, in view of a satisfactory intake, indicated good absorption from the intestine. On extremely high calcium intakes, several grams or more a day, a negative balance may be converted to a positive one; this has been the finding on short periods of study. It is my belief that such positive balances cannot be maintained in active cases of hyperparathyroidism; it is quite certain that clinical hyperparathyroidism is not to be permanently corrected by increasing the calcium intake.

Studies of calcium balance in hyperparathyroidism may be tremendously simplified by determining only the calcium excreted in the urine; as already stated, in hyperparathyroidism most of the calcium is excreted through the urine (as opposed to the excretion of calcium chiefly through the feces, normally). A convincing illustration of a negative calcium balance in generalized osteitis fibrosa cystica by such means was given by Snapper.[110] He employed a diet on which normal persons in control experiments excreted from 30 to 100 mg. of calcium daily in the urine. His patient with hyperparathyroidism excreted about 400 mg. of calcium before operation and about 25 mg. immediately after operation.

There is, however, less consistency in the results of the studies of phosphorus balance. For instance, a case of hyperparathyroidism studied by Hannon, Shorr, McClellan and DuBois,[28] in which a diet relatively high in calcium was given, showed conflicting results regarding the phosphorus balance; in five of the periods the balance was positive, while in the two final periods the balance was negative. The same patient, on a diet low in calcium, studied by Bauer, Albright and Aub,[118] showed consistent loss of phosphorus coincident with loss of calcium. An unusually high proportion of the phosphorus was excreted in the urine, and the loss of phosphorus was in close agreement with the loss of calcium. The same patient, when again observed by McClellan and Hannon [123] (a few months after the removal of two normal parathyroid glands at the Massachusetts General Hospital), showed that a positive phosphorus balance was maintained throughout the entire period of

122. Bulger, H. A.; Dixon, H. H., and Barr, D. P.: J. Clin. Investigation **9**:143, 1930.

123. McClellan, W. S., and Hannon, R. R.: J. Clin. Investigation **8**:249, 1930.

observation, even in those periods when there was definite loss of calcium from the body.

It must, however, be noted that a negative calcium and phosphorus balance is not a finding narrowly specific for hyperparathyroidism. For instance, in osteomalacia, there is, as Miles and Feng[124] showed, a negative balance for these substances. Nevertheless, the excessive loss of calcium and phosphorus is by way of the feces. Thus, the urinary excretion of calcium in this disease, unlike that in hyperparathyroidism, is diminished.

While it is true that studies of mineral balance are valuable in diagnosing Recklinghausen's disease, one must consider the handicaps which studies of short periods (as practiced at the present time) must of necessity introduce. It should be remembered that these studies of mineral balance as carried out currently can reflect in only the grossest manner the circumstances concerning the deposition or resorption of calcium and phosphorus with regard to the bones. That the present methods of testing for the loss of calcium and phosphorus from the skeleton are too inexact when the loss of these substances proceeds relatively slowly may be surmised from the work of Aub and Farquharson.[125] They had under observation cases in which there was great destruction and loss of bony substance (extensive metastatic carcinomatous nodules in the bones and advanced multiple myeloma), but the excretion of calcium and phosphorus in both the urine and the feces was within normal range for adults on a diet low in calcium during the periods studied.

Serum Phosphatase.—Phosphatase is an enzyme present in practically all the tissues of the body; it is found in large quantities in the intestinal mucosa, kidneys, leukocytes, cartilage undergoing endochondral ossification and connective tissue in which bone formation is in progress. This enzyme has the capacity for splitting organic phosphorus compounds and liberating inorganic phosphorus; at the same time, it possesses the ability to synthesize organic phosphorus compounds and to utilize inorganic phosphorus. Normally, phosphatase is present in small amounts in both the serum and the plasma of the blood. Larger amounts exist in the blood of infants and children than in that of adults. Kay,[126] who first systematically studied plasma phosphatase in a number of disorders, observed that it was abnormally increased in the plasma in some cases in which bone lesions were present (Paget's disease, active rickets, Recklinghausen's disease, etc.). Bodansky,[127] in this laboratory,

124. Miles, L. M., and Feng, C. T.: J. Exper. Med. **41**:137, 1925.
125. Aub, J. C., and Farquharson, R. F.: J. Clin. Investigation **11**:235, 1932.
126. Kay, H. D.: J. Biol. Chem. **89**:249, 1930.
127. Bodansky, A.: J. Biol. Chem. **101**:93, 1933.

developed a method for the determination of serum phosphatase which is free from a number of theoretical and practical objections which have been raised in regard to Kay's method. The values obtained by Bodansky's method, which are based on a large series of determinations, are estimated in units per hundred cubic centimeters of serum; normal children show from 5 to 12 units, and normal adults from 1.5 to 4 units. In a case of advanced Recklinghausen's disease the serum phosphatase value which Bodansky determined by his method was 20 units. Following the removal of a parathyroid adenoma, it dropped to about 10 units after a few months. It is extraordinary that the elevation of the serum phosphatase values in advanced cases of Recklinghausen's disease is nowise comparable to the extreme elevation of such values in cases of florid rickets or of disseminated florid Paget's disease. In this laboratory, values of 100 units or more were found in some active instances of the two last-mentioned conditions.

An analysis of the serum phosphatase values in many conditions in which bones were obviously affected (as obtained in this laboratory) has prompted the formulation of a particular conception of the mechanism underlying elevation of the level of the serum phosphate. This has been prepared for publication.[128]

Roentgenographic Aids in Diagnosis.—It is hardly necessary here to give a detailed discussion of the roentgenographic changes as they affect the skeleton; such details may be found in the articles of Dresser and Hampton,[129] Camp[130] and Kienböck and Markovits.[131] The disease is insidious in its development, evolving over a period of years and reaching advanced stages more rapidly in some patients than in others. Since patients may be examined in early or late stages, it is evident that the roentgenographic appearances may be quite different in any number of given cases. Since clinical diagnosis is now being made earlier, the advanced roentgenographic appearance of this disease (in which cysts and giant cell tumors may be seen) is less frequently encountered. However, no matter what the stage of the disease, the changes are more or less constant in one direction; that is, there is progressive thinning of the bones.

The roentgenologist, therefore, in interpreting roentgenograms showing generalized osteoporosis, should bear in mind the possibility that he is dealing with an early stage of Recklinghausen's disease. It must be promptly brought to attention that Recklinghausen's disease is

128. Bodansky, A., and Jaffe, H. L.: J. Clin. Investigation, to be published.

129. Dresser, R., and Hampton, A. O.: Am. J. Roentgenol. **25**:739, 1931.

130. Camp, J. D.: J. A. M. A. **99**:1913, 1932.

131. Kienböck, R., and Markovits, E.: Fortschr. a. d. Geb. d. Röntgenstrahlen **41**:904, 1930.

extremely rare. When a case in which generalized osteoporosis is present is suspected of being one of hyperparathyroidism, the final task of making the diagnosis must be given to the clinician and the clinical laboratory. The roentgenologist can safely make a diagnosis of Recklinghausen's disease only when the lesions in the bones are fairly advanced, and generalized osteoporosis, with cysts, giant cell tumors, fractures and a granular mottled appearance, is demonstrable in a few or in many bones.

Camp,[130] like others, recently stressed the miliary mottling and granular appearance of bones with advanced changes caused by hyperparathyroidism. This roentgenographic appearance was most prominently observed in the flat bones, especially the calvarium. He laid much stress on the presence of this granular mottling in making a diagnosis of Recklinghausen's disease. On pathologic grounds it is quite evident that the granular, mottled shadow cast by a bone changed by hyperparathyroidism is caused by a large quantity of new bone (consisting of thin, closely set, partially calcified trabeculae) which has replaced the original bone. Therefore, unless the resorption of the original bone has progressed to an advanced degree, and numerous newly formed trabeculae have appeared in the connective tissue which replaced the original bone, no granular, mottled shadow will be cast. For instance, in a long tubular bone, the progress of the lesions will be as follows: The original trabeculae become indistinct, and the cortical bone thins, so that a more or less homogeneous porotic shadow is cast before any semblance of a mottled, granular appearance occurs. Thus, while in any given case the appearance may be as Camp described it, the granular, mottled appearance applies only to bone that is in a certain pathologic stage.

The roentgen appearances of the skull may vary considerably in different cases. Visible deformities in contour may exist; softening of the bones at the base may cause flattening and diminution in the depth of the posterior fossa. The calvarium, however, presents the widest variations; it may be thinned and even have bony defects, a result of the osteoporosis. On the other hand, the calvarium may be thickened, either generally or irregularly. Irregular thickening is most often confined to the frontal, temporal or parietal regions. The details concerning the pathologic appearance of such a thickened area have been discussed; roentgenographically, the thickened portion of the calvarium shows the finely mottled, granular texture. The rest of the skull, including the facial bones, usually shows generalized osteoporosis; cysts and giant cell tumors may be observed in the mandible and maxillae.

The spine, as indicated in the description of the pathologic changes, may show marked deformities which are plainly evident roentgenographically.

Long tubular bones show progressive cortical thinning; expansion of the medullary cavity may appear. Cysts and giant cell tumors are sharply delineated, and may be surrounded by shells of bone. They have been observed even in the metatarsal and metacarpal bones. Infractions are frequently observed roentgenographically. Fractures (which are common) tend to unite readily, but excess callus is not seen. A cyst which has been the site of a fracture may show spontaneous healing. In advanced cases, the phalanges may show cortical resorption and even pathologic fractures. In children, many rachitic-like features may appear, such as bowing of the bones and slipping of the epiphyses. Roentgenographically, the metaphyses of the long tubular bones may be widened,[115] suggesting late rickets.

In view of the present status of the knowledge of Paget's disease, osteomalacia and senile osteoporosis, the diagnostic problems with which the roentgenologist has been confronted in regard to Recklinghausen's disease can, to a great degree, be put at rest. The differentiation between it and Paget's disease (especially as regards the long tubular bones) has been plain to many roentgenologists. Confusion between these diseases has occasionally arisen because of the relatively frequent thickening of the skull in Recklinghausen's disease. However, when the thickening of the skull is considered in conjunction with the rest of the bony changes there should be no confusion whatever between Recklinghausen's and Paget's disease. Most often, confusion has arisen between osteomalacia and Recklinghausen's disease, and this is sometimes pardonable. Osteomalacia, it should be remembered, does not have giant cell tumors and cysts—which may be present in Recklinghausen's disease. Furthermore, the resorption of the original bone is often not as pronounced in osteomalacia as it is in an advanced case of Recklinghausen's disease. Too much reliance should not be placed on deformity of the pelvis, for in advanced cases of this disease, the pelvis may be as badly deformed as in genuine osteomalacia.

DIFFERENTIATION FROM OTHER MALACIC DISEASES

The differentiation of Recklinghausen's disease from other malacic diseases has been greatly clarified in recent years, as a result of much progress in the comprehension of disturbances of mineral metabolism. There is therefore no need for discussing at great length the means of distinguishing the other generalized diseases of bone from this one.

Osteomalacia.—The condition with which Recklinghausen's disease has most often been confused is genuine osteomalacia. This perplexity

was rife before 1891,[1] and persisted for many years thereafter. Several enlightening considerations have contributed toward separating these diseases. The most important are: the proof that a deficiency of vitamin D is operative in the production of osteomalacia; the finding that Recklinghausen's disease is caused by hyperparathyroidism; the recognition that despite the apparent clinical similarity pathologic differences exist to differentiate these diseases. On microscopic grounds, the wide osteoid borders on the trabeculae, the absence of considerable fibrous tissue replacing the bone, the relatively infrequent presence of osteoclasts and the presence of a congested lymphoid marrow distinguish osteomalacia from Recklinghausen's disease. All these features have been discussed at length in the introductory and pathologic sections. It was pointed out that the cases described in the older literature as examples of osteomalacia with cysts and giant cell tumors are undoubtedly instances of Recklinghausen's disease.

In the United States, up to the present time, osteomalacia in its advanced form has been extremely rare; its incidence is probably even less than that of clinical hyperparathyroidism. Miles and Feng,[124] who studied the blood of osteomalacic patients (Chinese), whose illnesses had existed from less than one year to twenty years, found that in these cases there was considerable reduction in the serum calcium (5 to 7.4 mg. per hundred cubic centimeters); the serum phosphorus was from 1.8 to 3.8 mg. per hundred cubic centimeters. These investigators made metabolic studies of patients on a diet low in calcium, and found a negative calcium balance. Gargill, Gilligan and Blumgart [132] studied a case of osteomalacia at Boston, and also observed that on a diet low in calcium there was a negative calcium metabolism. This persisted even when the calcium ingested was excessive. Miles and Feng corrected the negative calcium balances in their patients merely by the administration of cod liver oil. Gargill, Gilligan and Blumgart found that their patient would not store calcium and phosphorus (indicative of healing) until they administered as large quantities as 100 cc. of cod liver oil concentrate daily.

While the condition of the parathyroid glands may be completely normal in osteomalacia (which is never the case in Recklinghausen's disease), occasionally slight enlargement of all the parathyroids may be encountered, while even more infrequently one of these glands may reach a fairly large size. Parathyroid enlargement in osteomalacia must be looked on as secondary to the bone disease and therefore compensatory. Erdheim [13] contended that even when the parathyroids are

132. Gargill, S. L.; Gilligan, D. R., and Blumgart, H. L.: Arch. Int. Med. **45**:879, 1930.

not grossly enlarged, microscopic evidences of hyperplasia can be ascertained by special methods of histologic examination.

There need be no confusion of Recklinghausen's disease with genuine infantile rickets. However, in adolescent children, Recklinghausen's disease may produce bowing deformities of the lower extremities with widening of the metaphyses; these may be observed roentgenographically. This would introduce some possibility of mistaking this disease on clinical grounds for adolescent rickets. The parathyroids themselves are not enlarged in most cases of infantile or of late rickets.[133]

Paget's Disease.—The distinction between Recklinghausen's disease and Paget's disease has already been well covered. Christeller's [51] concept that the former is the "hypostotic," and the latter the "hyperostotic," form of fibrous osteodystrophy is now completely dissipated. Recklinghausen's disease is a generalized condition, and this feature is further opposed to the localized (although polyostotic and progressive) character of Paget's disease. The participation of the periosteum in the production of the pathologic lesions of Paget's disease is in contrast to the lack of periosteal activity in hyperparathyroidism. Lamellation of the cortex of long tubular bones of the type seen in florid cases of Paget's disease does not occur in Recklinghausen's disease, in which the cortex is thinned. The general character of the bony thickening and deformity observed in Paget's disease is not seen in Recklinghausen's disease. Giant cell tumors of the nature observed in Recklinghausen's disease do not occur in Paget's disease. The parathyroid glands lack the tumorous enlargement that is seen in Recklinghausen's disease. If the parathyroid glands are at all enlarged, the enlargement is slight, generalized and of a secondary, compensatory nature. The clinical examinations of the blood have shown no particular abnormalities in Paget's disease; furthermore, studies of mineral balance have given no constant results. In a recent summary, I [134] have detailed the anatomic and clinical features of Paget's disease which distinguish it from Recklinghausen's disease.

Generalized Osteoporosis: Senile Osteoporosis.—I wish to make clear that the so-called "inactivity atrophy or osteoporosis" and "hunger osteopathy or osteoporosis" are entirely excluded from consideration here. Furthermore, the osteoporoses secondary to endocrinous disturbances (hyperthyroidism, obesity associated with basophilic pituitary adenoma, etc.) are also excluded from this discussion. This leaves a large group of cases (senile osteoporosis) in which such pronounced rarefaction of the skeleton may occasionally occur that roentgenographic

133. Schmorl, G.: München. med. Wchnschr. **54**:494, 1907.
134. Jaffe, H. L.: Arch. Path. **15**:83, 1933.

study of the bones may suggest the presence of Recklinghausen's disease. Such bones are very transparent to roentgen rays, are brittle and may fracture.

The conditions operating to produce this type of osteoporosis are related to the general involutionary process that occurs in all aging and senile persons. Senile osteoporosis has been studied particularly by the older pathologists. Pommer's [56] concept that in senile persons physiologic deposition of new bone is decreased while physiologic resorption continues at a normal pace, so that over a period of years progressive thinning of the bones occurs, is the view that generally prevails as to the pathogenesis.

It is well known that in aged persons senile osteoporosis of the neck of the femur is the reason for its frequent fracture. In such cases, fibrous transformation of the bone, limited to the site of fracture, may be observed. Involvement of the spine, particularly the vertebral bodies, leads to kyphosis and sometimes even to greater deformities. Owing to weakening of the bony structure of the bodies, expansion of the intervertebral disks is common. With expansion of the intervertebral disks, collapse of the internal architecture of some of the bodies (which are reduced in their superior-inferior dimensions) results in proliferation of new bone in the proliferated osteogenic connective tissue. Otherwise, marrow fibrosis and new bone formation are not a part of the uncomplicated pathologic changes in senile osteoporosis.

In other words, the pure lesion is simply a chronic fatty atrophy of the bone; the trabeculae and cortex are thinned; the marrow cavity of the tubular bone increases in size; the canals of the blood vessels of the cortex are widened; the periosteal surface of the cortex is smooth; microscopic lacunar resorption is negligible; osteoid borders are not demonstrable; the fat in the marrow cavities is soft and oily. If fibrous transformation of the marrow occurs, associated with the appearance of connective tissue new bone in the fibrosed marrow, it is localized in areas in which there has been collapse of the spongy bone.

Pain from pressure on the bones is usually absent in senile osteoporosis, but in very pronounced cases it may be found; in such cases the condition has progressed to such a serious state that advanced thoracic deformities exist, which may be combined with curvature of the lower extremities and which, clinically, may produce a picture suggestive of Paget's disease. Aside from the clinical suggestion, these diseases are not in the least related.

On histologic grounds, senile osteoporosis is to be distinguished from osteomalacia and Recklinghausen's disease because there are no osteoid borders, giant cell tumors, marked lacunar erosions or the type of cysts seen in Recklinghausen's disease. In the long tubular bones of such

patients more or less large brown areas, containing hemosiderin, are occasionally seen and are referable to recent hemorrhage. Microscopically, however, accumulations of giant cells are not observed in such areas. Thus, there are no genuine brown tumors in an osteoporosis which is not caused by hyperparathyroidism. In advanced cases of senile osteoporosis, small, single and confluent cysts may be observed in some of the long tubular bones; these are nothing more than oily cysts due to liquefaction of the fatty marrow. The walls of such cysts consist of connective tissue, surrounded by normal or somewhat modified fat cells. These cysts are well illustrated in the cases of Gerth [135] and Schupp.[40] Such advanced stages of senile osteoporosis are indeed rare.

The parathyroid glands play no part in the pathogenesis of this condition; when studied, they were often found to be normal. They have occasionally been reported as showing enlargement, recognized by the naked eye. At such times, they are dark red or brownish; if the enlargement is not actual, it may be considered to be relative to the atrophy of the other organs and tissues. Maresch [18] observed a case of senile osteoporosis in which one gland measured 12 by 8 by 6 mm., and which microscopically showed foci of hyperplastic proliferation.

"Fibrocystic Disease" of Problematic Origin.—It seems eminently desirable at this point to review several reported cases which, in my opinion, constitute a doubtful group; these are open to confusion with either Recklinghausen's or Paget's disease. One such case was recently described by Bradfield.[136] The patient first came under observation in 1913 at the age of 6 years; at that time he suffered from a fracture of the right femur. The disease progressed in the lower extremities between the ages of 6 and 9, and several fractures occurred in the femora and tibias; it was still active in the right humerus at the age of 18. At the time of the report it was believed that the disease was no longer active, although the major skeletal changes did not seem to be correcting themselves. On roentgenographic study, the skull was suggestive of Paget's disease, while the long tubular bones appeared thin and cystic. In 1921, a fragment of the right femur was removed and studied histologically; it showed the presence of considerable cartilage; no gross cysts or giant cell tumors were observed. At no time did any clinicopathologic investigations throw light on the etiology of the condition. Elmslie,[137] who had reported the clinical aspects of this case in 1914, also examined the biopsy slides from the specimen obtained in 1921; he confirmed the histologic findings reported by Bradfield. He further stated, in a concluding note to Bradfield's paper, that he had recently studied another case in

135. Gerth: Virchows Arch. f. path. Anat. **277**:311, 1930.

136. Bradfield, E. W. C.: Brit. J. Surg. **19**:192, 1931.

137. Elmslie, R. C.: Brit. J. Surg. **2**:17, 1914.

which the pathologic picture was similar to that alluded to; no parathyroid tumor was found on surgical exploration of the neck, and the serum calcium and phosphorus values were within the normal range.

Hirsch [138] had previously discussed another example of this condition (in many ways completely duplicating the one detailed by Bradfield). The patient was first seen in 1912, at the age of 15. The salient features of the recorded history are as follows: A slight protuberance was noted over the right parietal bone at the age of 8; another soon developed in the left cheek; the size of the head increased (from the age of 8); curvature of the spine developed early. Between 18 and 27, fracture of the clavicle and fractures of the ribs occurred; at 23, the right femur fractured. In spite of this record, in 1929 when Hirsch made his report, the patient's general health was good; the serum calcium was 10.9 mg. and the serum phosphorus 4.2 mg. Thus, during the fifteen years of observation by Hirsch, the roentgenographic lesions in the long bones showed no striking changes from their original appearance, while those in the metacarpal and phalangeal bones showed a tendency toward healing. The skull, since the inception of the lesions at 8 years, had shown a progression of the changes in the direction of Paget's disease.

Still another case of a generalized disease of bone (that Willich [139] described as an instance of "spontaneous healing in a generalized osteodystrophy") probably falls into this category. Thirty years previous to his report, the disease was ushered in with swelling of the jaw and pain in the tibia. By 1912, all the roentgenographic appearances were considered those of a generalized osteitis fibrosa; between 1912 and 1928, all the bones, with the exception of the skull, had shown considerable spontaneous regression of the lesions. In spite of all this, the skull, which shows changes like those in Paget's disease, has been increasing in size during the last few years.

Telford [140] also recently reported an instance of what seems to be a local manifestation of the same condition (the pathologic lesions are apparently localized in the bones of the left lower extremity). The patient, a woman 34 years of age, was well until 14, when the left femur fractured. Several years before the report, swelling of the left lower extremity with enlargement of some of the bones appeared. Histologic sections of a biopsy specimen evidenced the presence of large amounts of hyaline cartilage; this was likewise the feature in the specimen in Bradfield's case.

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138. Hirsch, I. S.: Radiology **12**:505; **13**:44, 1929.
139. Willich, C. T.: Beitr. z. klin. Chir. **146**:103, 1929.
140. Telford, A. D.: Brit. J. Surg. **18**:409, 1931.

My impression is that these conditions are neither Recklinghausen's nor Paget's disease, and that they constitute a still unidentified entity. I strongly suspect that they have a congenital basis.

Renal Rickets.—Renal rickets, while not offering any real difficulties in differential diagnosis from Recklinghausen's disease, is a condition that probably results from a disturbance in the metabolism of calcium and phosphorus (for which the underlying chronic nephritis is evidently responsible). While albuminuria, associated with deformities of the extremities in children, has been known for a long time, the dependence of the changes in the bones on the renal disease was stressed in 1911 by Fletcher.[141] Fishberg [142] thinks that the changes in the bones may be attributed to the fact that, associated with renal disease in general, there are chronic acidosis and a diminished ability on the part of the kidney to form ammonia; in consequence of an inadequate formation of ammonia, the organism is forced to excrete fixed base. This is mobilized from the bones, and to this he refers the pathogenesis of the bony lesions of renal rickets. The recent observation by Boyd [143] seems to be in harmony with this conception. He reported an instance of rachitic-like lesions developing in a child of 10 years (subsequent to transplantation of the ureters into the rectum). Chronic acidosis developed, and this was associated with roentgenographic appearances suggestive of rickets. The changes in the bone were corrected by the daily administration of large doses of sodium bicarbonate; they were therefore the result of an acidosis, but since the acidosis could be corrected, the lesions healed.

In this connection, it may be interesting to note the observation made by MacCallum [17] in 1905; at autopsy on a young patient with chronic nephritis he found a parathyroid tumor about 2 cm. in diameter; the bones were not studied. It is quite likely that the enlarged parathyroid was the result of a compensatory hypertrophy. Bergstrand [38] more recently has noted that resorption of bone occurs in some cases of chronic nephritis. The ribs of a subject, 17 years of age, who died of chronic glomerulonephritis, showed considerable lacunar resorption; a man, aged 58, who died of chronic glomerulonephritis, had advanced lacunar resorption of the femoral diaphysis and a bean-sized parathyroid adenoma. In regard to parathyroid enlargement in chronic nephritis, Bergstrand [15] stated on another occasion that about 10 per cent of the cases may show secondary parathyroid hyperplasia.

Certain Local Lesions: Their Relation to Recklinghausen's Disease.—Consideration is here given to certain local lesions, such as solitary

141. Fletcher, H. M.: Proc. Roy. Soc. Med. (Sect. Child. Dis.) **4**:95, 1910-1911.

142. Fishberg, A. M.: Nephritis and Hypertension, Philadelphia, Lea & Febiger, 1931, p. 417.

143. Boyd, J. D.: Am. J. Dis. Child. **42**:366, 1931.

giant cell tumors, single unilocular or multilocular cysts and the various forms of so-called localized osteitis fibrosa cystica.

Solitary giant cell tumors most frequently appear in the epiphyses of tubular bones (especially the long tubular ones), although they may be observed in flat bones, in the vertebrae and even in the diaphyses or beneath the periosteum of tubular bones. These tumors, which consist of a very vascular spindle cell stroma and varying numbers of multinucleated giant cells (osteoclast type), in many respects histologically resemble the giant cell tumors of Recklinghausen's disease. Localized giant cell tumors may extend to beneath the articular cartilage and may then destroy portions of the bony end-plate; by confluence of foci, the entire bony end-plate may be destroyed; sometimes foci enter the articular cartilage. I have observed such tumors breaking into a joint. However, as was pointed out in the pathologic section, I believe them to be true blastomas and therefore not analogous to the giant cell masses of Recklinghausen's disease.

Single unilocular or multilocular cysts generally occur in the metaphyses of the long tubular bones of very young children, but may also extend into the epiphyses of such bones. Cartilaginous proliferations are occasionally observed in such cysts, but these have no connection with the original epiphyseal cartilage plate. The significance of such cartilaginous proliferations is unknown; whether they should be interpreted as callus formations or as displaced cartilaginous nests (which occur normally in the head of the femur) remains to be decided. Larger cartilaginous masses undergo cystic degeneration; this led Virchow to consider such cysts the end-results of degeneration of enchondromas. The presence of large masses of degenerating cartilage is rather the exception than the rule in simple benign cysts of bone. These localized cysts constitute a distinctive group, also not to be confused with the cysts of Recklinghausen's disease.

The various forms of so-called localized osteitis fibrosa cystica may be nothing more than delayed or otherwise abnormal and perverted healing processes (secondary to infection or trauma) or part of a healing reaction in a giant cell tumor or cyst.

Particular emphasis should be laid on the fact that no matter how closely the gross and histologic appearances of these lesions approach certain of the pathologic aspects of Recklinghausen's disease, they are in no way to be considered etiologically or pathogenically identical. Furthermore, while cystic degeneration of giant cell masses may occur in Recklinghausen's disease, there is absolutely no reason for considering solitary unilocular or multilocular cysts as the end-result or the healing stage of solitary giant cell tumor—the conception popularized in this

country by Geschickter and Copeland.[144] The serum calcium and phosphorus values are always within normal range in these conditions, as is the serum phosphatase, and those who have studied the mineral metabolism (for calcium and phosphorus) have also found no deviation from the normal. These conditions are not associated with tumorous hypertrophy of the parathyroid glands, and removal of normal parathyroid tissue does not alleviate them, if additional local procedures are not instituted.

When a patient presents what appear to be multiple, benign, giant cell tumors, there is always the possibility that the condition is Recklinghausen's disease. This is borne out by the report of an instance of multiple giant cell tumor made by Alexander and Crawford[145] in 1927; it was subsequently reported as one of proved hyperparathyroidism.[111] Even today, the danger exists of treating some of the aspects of Recklinghausen's disease as purely local disturbances. Recently, a case was reported in which the femur of a young woman was amputated because of the persistence of nonunion (for five months after a fracture). The fracture occurred through a cystic lesion, the nature of which was at first unconnected with Recklinghausen's disease. Two months after amputation, roentgenographic examination of all the long bones disclosed a generalized disease, and at operation a parathyroid tumor was removed.[146]

TREATMENT

Parathyroidectomy: Results.—Beginning with Mandl,[24] it was shown that whenever a clearcut case of hyperparathyroidism had been diagnosed removal of one or more parathyroid adenomas usually resulted in immediate marked clinical improvement. Relief from pain has been one of the most striking postoperative effects; some of the patients were bedridden, but became ambulatory soon after operation. In many instances there was a prompt change from the negative calcium balance to a state of equilibrium or to an even positive balance; usually, return of the serum calcium and phosphorus values to normal was also noted; in many instances, roentgenograms have shown evidences of recalcification of the skeleton, even to the point of disappearance of cysts and giant cell tumors. Deformities do not show early spontaneous correction of any proportion; spontaneous correction of deformities in adults must take a very long time (because of the slow reconstruction that goes on in the adult skeleton).

144. Geschickter, C.; Copeland, M. M., and Bloodgood, J. C.: Arch. Surg. **19**:169, 1929.

145. Alexander, E. G., and Crawford, W. H.: Ann. Surg. **86**:362, 1927.

146. Taylor, G. G., and Wiles, P.: Brit. J. Surg. **19**:606, 1932.

I have communicated with a number of those who reported cases of hyperparathyroidism in which parathyroidectomy was done. Hunter, who with Turnbull,[147] described four personally observed cases in comprehensive detail, wrote that the cases show further consistent progression of the healing since the report was published. Compere's [148] patient has done exceedingly well, as has Pemberton and Geddie's.[113] From others, I have likewise received communications confirming continued improvement.

The need for perseverance and persistence in the search for the offending parathyroid adenoma is well illustrated in the case reported by the Cornell and Harvard medical school groups. Several references were made in foregoing pages to this case,[149] and its remarkable course was recently summarized by Bauer.[150] Hitzrot and

147. Hunter, D., and Turnbull, A. M.: Brit. J. Surg. **19**:203, 1931.

148. Compere, E. L.: Surg., Gynec. & Obst. **50**:783, 1930.

149. Hannon, Shorr, McClellan and DuBois.[28] Bauer, Albright and Aub.[118] McClellan and Hannon.[123]

150. "This patient, a sea captain, was first recognized as a case of hyperparathyroidism by Dr. Eugene F. DuBois of New York in 1926. He has suffered from eight fractures. He has a marked kyphosis, considerable skeletal shortening and permanent bone deformities. His serum calcium has ranged between 13.1 and 16.5 mg. per 100 cc. The serum phosphorus varied from 1.4 to 3.2 mg. per 100 cc. The calcium and phosphorus excretions were markedly elevated. He was operated upon by Dr. E. P. Richardson in May, 1926, and in June, 1926. At each operation a parathyroid gland was removed, normal in appearance, but microscopic examination showed fatty infiltration. Removal of these two glands did not result in a cure, and the serum calcium and phosphorus, as well as the total calcium and phosphorus metabolism studies, remained unchanged. Despite a high calcium diet his symptoms and signs increased to such an extent that a third search was made for a parathyroid tumor in March, 1932, by Dr. Russel H. Patterson of New York City, but again no tumor was found. He was again transferred to the Massachusetts General Hospital in May, 1932. Examination at this time showed considerable increase in the severity of his disease. The decalcification had increased; there were many more bone cysts; questionable calcification of the kidney cortex (demonstrable on flat x-ray plate of the abdomen); kidney and ureteral stones; hypercalcemia and hypophosphataemia. Kidney function tests showed marked renal impairment evidenced by a non-protein nitrogen of 60 mg. per 100 cc. and a phenolsulphonphthalein excretion of 10 per cent in two hours' time. At three subsequent operations by Dr. Oliver Cope and Dr. E. D. Churchill, careful dissections of the various regions of the neck between the angles of the jaw and upper mediastinum were made; yet no parathyroid tumor or tissue was found. On November 2, 1932, an anterior mediastinotomy was done by Dr. E. D. Churchill. The parathyroid tumor, encased in a calcified capsule, was found; 90 per cent of it was excised, the remainder of the tumor was turned up on its pedicle and sewed in a superficial position in the region of the sternal notch. The serum calcium fell rapidly, and signs of tetany appeared on the third day. At this writing the serum calcium continues to fluctuate between 4.5 and 7.2 mg." (Bauer, W.: J. Bone & Joint Surg. **15**:135, 1933.) Since then the patient has died, and postmortem study confirmed the presence of the bone changes of hyperparathyroidism.

Comroe [151] reported a case of osteoporosis, most likely caused by hyperparathyroidism, in which three normal parathyroid glands were removed. It seems to me that in all probability the condition will become progressively worse, as an undiscovered parathyroid adenoma surely exists.

The conclusive and dramatic effects so often obtained by the removal of adenomatous parathyroid tissue are not always sustained over an appreciable interval. The case reported by Boyd, Milgram and Stearns [112] is one in point. Dr. Boyd, in a recent personal communication (November, 1932), wrote:

> Eighteen months after operation, this patient offered clinical, chemical and roentgenological evidence of relief from his condition. Bilateral osteotomies had been performed, and perfect healing had resulted. The density of the bones had returned to normal limits, so far as roentgenograms indicated. About six months ago, he returned to the hospital at our request, to serve as his own control for the completion of his metabolic study. It was discovered that his serum calcium against approximated 16 mg., his inorganic phosphorus 2.5 mg., per 100 cc. Other chemical data indicated a recurrence, yet there is no evidence of bone disease at present. Some general symptoms of hypercalcemia are becoming evident. He is now in the hospital under observation, and we hope soon to present for publication these findings that I have described to you, together with detailed metabolic data.

It may well be that in this case an additional parathyroid tumor exists. Heilstroem [152] described a case in which there was temporary relief following the extirpation of an adenoma the size of a walnut; recurrent symptoms were entirely relieved by the removal of another parathyroid adenoma of about the same size. The case reported by Quick and Hunsberger [111] definitely showed that improvement is not to be expected if any of the adenomatous tissue is left behind (as in their case, owing to rupture of the enlarged gland during a difficult removal).

Postoperative Complications.—Removal of one or more parathyroid adenomas in the surgical treatment of these conditions has frequently been followed by parathyroid tetany. Often, on the day following operation, numbness and tingling in the fingers and toes occur; this may become worse; Chvostek's sign may appear together with other evidences of parathyroid tetany (prompt drop of the serum calcium). (The danger of tetany may possibly be reduced by a two-stage operation in which the adenoma or a part of it is first transplanted into the abdominal wall and removed several weeks later.) Precautions should therefore be taken immediately after operation to prevent the onset of tetany. Large amounts of calcium by mouth in the form of calcium lactate or other soluble calcium preparations are often effective. Owing to the rapid elimination of calcium, frequent administration is a desirable feature

151. Hitzrot, L. H., and Comroe, B. I.: Arch. Int. Med. **50**:317, 1932.
152. Hellstroem, J.: Acta chir. Scandinav. **69**:237, 1932.

of the calcium treatment (about every two or three hours). The dose should be large, as much as several grams of calcium daily (1 Gm. of calcium lactate is equivalent to approximately 130 mg. of calcium). When prompt effects are required, intravenous injection of from 5 to 10 cc. of calcium chloride may be necessary (10 per cent solution, slowly administered, leakage into surrounding tissues being avoided).

Owing to the rapid elimination of ingested or injected calcium, tetany may nevertheless develop. Therefore an agent which acts more slowly and the effect of which continues longer than the effect of ingested or injected calcium would be desirable in conjunction with the use of calcium. Parathyroid extract-Collip satisfies that requirement, and it has been used successfully when administration of calcium alone failed to prevent or to correct the tetany. Ten or 20 units of parathyroid extract may be given three or four times daily (subject to control by the determination of serum calcium). In addition, large therapeutic doses of viosterol may also be used. Such treatment may be continued for a number of weeks until the serum calcium values are definitely above the tetanic level. A low normal value of serum calcium may be stated as 9 mg. per hundred cubic centimeters. At a serum calcium value sufficiently close to that, there would be no danger of tetany due to hypocalcemia. Immediately after the operation, before adjustment has been accomplished, symptoms of tetany have been observed despite the fact that the serum calcium and phosphorus values were not sufficiently different from the normal to account for the tetany. Later, in one such case, the serum calcium fell to very low levels, and the injection of parathyroid extract-Collip and the administration of calcium by mouth proved ineffective until calcium was given intravenously (Barr and Bulger [29]). It is evident that the early management after the operation must vary with each case.

The reason for the development of the hypocalcemia and parathyroid tetany is not easily apparent; there has been much speculation on the mechanism of their appearance in clinical cases. Bodansky and I [31c] observed hypocalcemia in guinea-pigs several days after the discontinuance of prolonged treatment with parathyroid extract-Collip. We believed that this was most probably due to rapid redeposition of calcium in previously depleted tissues, associated with changes in the phosphorus balance. We also suggested that in experimental animals a temporary hypofunction of the normal parathyroid glands may have been caused by the prolonged treatment with parathyroid extract-Collip; immediately after the termination of the state of experimental hyperparathyroidism, hypofunction of the normal parathyroid glands contributed to the production of the complex of hypocalcemia, hyperphos-

phatemia and a positive calcium and phosphorus balance, a complex which is often observed during the period of recovery in clinical cases. The same explanations were suggested for the analogous developments following the removal of parathyroid adenoma in Recklinghausen's disease.

Another common and disconcerting complication is oliguria, which may develop immediately after operation. Its cause is not known; When it occurs it corrects itself after a few days.

Attempts at Nonsurgical Treatment.—After the successful operative treatment had been established on a sound footing, and when the metabolic disturbances in hyperparathyroidism were better understood, some attempts were made to control the disease by nonsurgical measures. These attempts logically followed the advances in the understanding of the metabolic features in this disease; the reasons for undertaking such measures could well be understood in view of the existing general knowledge of mineral metabolism; however, certain of these nonsurgical measures (phosphate treatment) are not to be employed, as they may even aggravate the condition of patients with hyperparathyroidism. Therefore, when hyperparathyroidism is established in a patient, operative search for a parathyroid tumor should be undertaken as soon as the patient's condition warrants. I do not believe that it is a good policy to attempt to destroy such a tumor by irradiation.

The form of nonsurgical intervention on which most hope had been based was treatment with phosphates. Experience in administering phosphates in the form of sodium acid phosphate led Bulger, Dixon and Barr [122] to suspect, from a theoretical point of view, important therapeutic possibilities. It seemed probable to them that if sufficient phosphate could be absorbed, serum phosphate might be increased and serum calcium lowered; if this alteration could be accomplished, they thought that the calcium metabolism might be restored to normal. Albright, Bauer, Claflin and Cockrill [153] also investigated the effects of ingestion of phosphate in clinical hyperparathyroidism (using monosodium phosphate and forcing fluids). They reported that the net result of such treatment is a tendency toward a positive balance of calcium phosphate and the alteration of the serum calcium and phosphorus values in the direction of normal. While a correction of the calcium-phosphorus metabolism may be attained by such measures, the effects are only temporary and, as pointed out,[153] not without danger. (The danger would be especially great if the serum phosphorus were elevated above normal; this would probably hasten death by increasing the supersaturation of the blood with phosphorus. Another danger of the ingestion of phos-

153. Albright, F.; Bauer, W.; Claflin, D., and Cockrill, J. R.: J. Clin. Investigation **11**:411, 1932.

phate is that it may aggravate the tendency to the formation of renal stones by increasing the phosphaturia). The condition of a patient on whom phosphate therapy was tried by these workers [153] nevertheless became progressively worse over a period of years; the course was summarized by Bauer.[154]

In unpublished experiments, Bodansky and I have used phosphates in an effort to relieve dogs of the toxic effects of acute hyperparathyroidism. Sometimes, the results were startling; apathetic dogs, apparently moribund, would be relieved of the ill effects of overdosage of parathyroid extract within a few hours, and show a sharp drop in the serum calcium; at other times, the dogs died in spite of this treatment. At autopsy, congestion of the intestinal tract and metastatic calcification were observed; these changes are clearly established as being associated with fatal, acute hyperparathyroidism. The deleterious effects of phosphates in animals suffering from chronic hyperparathyroidism were recently further shown by the experiments of Grauer.[155] He stated that the intraperitoneal injection of sodium acid phosphate (from 0.25 to 1 cc. of a solution containing 0.075 Gm. per cubic centimeter) in guinea-pigs simultaneously receiving parathyroid extract-Collip exaggerated the decalcifying effects.

Viosterol has been used to promote recalcification of bone following removal of a parathyroid tumor. However, some have attempted to utilize it for nonoperative control of cases of Recklinghausen's disease; it seems to have no effect on the disease under such circumstances. In experimental hyperparathyroidism, Johnson [156] found that it did not prevent decalcification of the bones of either rats or dogs; if anything, the lesions were worse in the animals given viosterol. Likewise, Bodansky, Blair and I [157] noted that viosterol could not protect guinea-pigs from the demineralizing effects of parathyroid extract-Collip.

154. Bauer, W.: J. Bone & Joint Surg. **15**:135, 1933.

155. Grauer, R. C.: Proc. Soc. Exper. Biol. & Med. **30**:57, 1932.

156. Johnson, J. H.: Am. J. M. Sc. **183**:776, 1932.

157. Jaffe, H. L.: Bodansky, A., and Blair, J. E.: Proc. Soc. Exper. Biol. & Med. **29**:202, 1931.

Notes and News

University News, Promotions, Resignations, Appointments, etc.—According to *Science*, Felix d'Herelle has resigned from the professorship of bacteriology which he has held at Yale University since 1927. While in residence Dr. d'Herelle confined himself largely to the study of bacteriophagy as a laboratory phenomenon, since suitable clinical material was lacking. It is the hope of elaborating his work in the clinical field, possibly at the new institute for infectious diseases at Tiflis, Russia, which now takes him abroad.

At Yale University H. M. Zimmerman has been promoted to a professorship of pathology.

In George Washington University E. B. Vedder has been appointed professor of experimental medicine and executive officer of the department of pathology and experimental medicine; J. L. Snyder has been appointed instructor in pathology, and Roger M. Choisser has been appointed professor of pathology.

Richard F. Thompson has been made assistant professor of bacteriology in Columbia University, New York.

The retirement on October 1 of Edwin O. Jordan as chairman of the department of hygiene and bacteriology in the University of Chicago has been announced. Dr. Jordan began his service in the University in 1892 and has been professor of bacteriology since 1907. He will be succeeded as chairman by William T. Taliaferro, professor of parasitology.

Edward L. Miloslavich, Milwaukee, has been appointed professor of legal medicine and director of the medicolegal institute at the Royal University of Zagreb, Jugoslavia.

Society News.—The second conference of the International Association for Geographic Pathology will be held in Utrecht during the last week of July, 1934, under the presidency of D. J. Josselin de Jong. The main topic of the conference will be arteriosclerosis; cirrhosis of the liver will be considered also. The association now has committees in twenty-eight countries. The executive committee consists of D. Josselin de Jong, Utrecht; Ludwig Aschoff, Freiburg-i-B.; Max Askanazy, Geneva; H. T. Karsner, Cleveland, and Gustaf Roussy, Paris. The chairman of the committee for the United States is Virgil H. Moon, Jefferson Medical College, Philadelphia. The annual dues are $2.35 (10 Swiss francs). Each member receives a copy of the transactions. Membership is open to all who are interested.

The Third International Congress for Experimental Cytology will be held in Cambridge, England, August 21 to 26, 1933.

Carl V. Weller has been elected president, S. B. Wolbach president-elect, and C. P. Miller, Jr., secretary, of the American Society for Experimental Pathology.

At the twenty-sixth annual meeting of the American and Canadian Section of the International Association of Medical Museums, Victor C. Jacobsen was selected president, William Boyd vice-president and Maude A. Abbott secretary-treasurer.

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

EFFECT OF ROENTGEN RAYS ON THE CENTRAL NERVOUS SYSTEM. R. S. LYMAN, P. S. KUPALOV and W. SCHOLZ, Arch. Neurol. & Psychiat. **29**:56, 1933.

Roentgen irradiation caused in four dogs both physiologic and structural changes. The former have been determined by observation of conditioned reflexes, which showed that diffuse cortical and subcortical changes had occurred. Histologic changes were also present, in the form of necrosis of scattered regions of the brain — occipital lobe, basal ganglions and optic chiasm.

Scholz, who studied the brains anatomically, sees the origin of the changes in the damage that irradiation is supposed to cause in the blood vessels — hyalinization and obliterating sclerosis — but not in the irradiation itself or in the possible inflammatory phenomena.

G. B. HASSIN.

CHROMATOLYSIS OF EFFERENT NEURONS. FREDERICK D. GEIST, Arch. Neurol. & Psychiat. **29**:88, 1933.

Geist studied in paraffin and celloidin sections the ganglion cell changes in various spinal and cranial nerves of monkeys and rabbits. The changes — chromatolysis or breaking up of the chromophilic granules — varied. The granules may undergo rearrangement; the cell itself may shrink, enlarge or fail to undergo any changes, and the nucleus may not change its location. The main factors instrumental in the ganglion cell changes are the type and age of the animal used and the distance from the central nervous system at which the nerve is injured.

G. B. HASSIN.

SUBARCUATE FOSSA OF TEMPORAL BONE OF MAMMALS: MORPHOLOGIC AND EMBRYOLOGIC RESEARCHES. L. CIURLO, Arch. ital. di otol. **43**:707, 1932.

Ciurlo made a study of the subarcuate fossa in the cranium of the human adult and fetus and many mammals. He describes its variations and its relations to the meninges, the cerebellum and the choroidal plexus of the fourth ventricle. He gives the details of the fossa in the embryos of cats, dogs, bats, etc., at different periods of their development. In the embryos of these mammals the subarcuate fossa is filled with mucous tissue and many small veins. It is only after birth that it is occupied by a lobule of the cerebellum. The veins of the fossa represent a branch of the posterior cerebral vein connected with the internal jugular vein. At an indeterminate time this branch is anastomosed with the superior petrosal sinus and forms its most internal portion.

NASAL FACTOR IN GENESIS OF ANAPHYLACTIC BRONCHIAL ASTHMA: CLINICAL OBSERVATIONS AND TREATMENT. E. RUBALTELLI, Arch. ital. di otol. **43**: 738 (Dec.) 1932.

Rubaltelli studied a large number of patients with anaphylactic bronchial asthma, and found in a large percentage of them, besides nasal stenosis, a peculiar change in the form and structure of the ethmoid. Considering the nose as an organ of respiration and a reflex center, the author discusses the possibility of the direct and indirect mechanisms through which the nose may occupy first place in the etiology and pathogenesis of anaphylactic bronchial asthma. He concludes that in reality the nose holds an important place in the origin of this allergic disease,

either by the changed permeability of its mucosa or by its power of originating reflexes. From the therapeutic point of view, he asserts that prudent and partial operations on special portions of the nasal mucosa ameliorate the course of anaphylactic bronchial asthma because they reduce the zone of possible origin of the reflexes and modify the altered permeability of the mucosa itself.

HYPERTENSION AND MALIGNANT NEPHROSCLEROSIS IN NEGROES. R. H. JAFFÉ. Centralbl. f. allg. Path. u. path. Anat. **55**:209, 1932.

This report concerns the frequent occurrence of nephrosclerosis in Negroes, over 20 years of age, and serves to indicate the racial and sex incidence of this disease in 2,144 necropsies.

TABLE 1.—*Incidence of Malignant Nephrosclerosis*

		Malignant Nephrosclerosis	
	No. Autopsies	No. Cases	Per Cent
White men	972	9	0.92
White women	367	5	1.3
Negro men	476	24	5.0
Negro women	329	26	7.9

TABLE 2.—*Age Incidence*

	Under 60 Years, Per Cent	Average Age, Years
White men	88	50
White women	100	39
Negro men	96	42
Negro women	89	42

TABLE 3.—*Incidence of Hypertension*

	Number with Hypertension	Per Cent of Autopsies	Per Cent of Cases of Malignant Nephrosclerosis
White men	260	26.7	3.4
White women	86	23.4	5.6
Negro men	175	36.7	13.7
Negro women	102	31.0	25.4

The theory that Jaffé advances to explain the frequency of malignant nephrosclerosis is based on the change of climate experienced by Negroes who came from southern states to Chicago. Most of the Negroes dying of nephrosclerosis had been in Chicago only a short time.

GEORGE RUKSTINAT.

THE SECRETING TYPE, A MENDELIAN CHARACTERISTIC DEMONSTRABLE BY SEROLOGIC METHODS. F. SCHIFF and H. SASAKI, Klin. Wchnschr. **11**:1426, 1932.

Persons possessing agglutinogens A and B may secrete them in a concentrated form in the saliva, as may be shown by inhibition tests. The agglutinable factor of group O blood may also be demonstrated in saliva. Not all persons secrete antigens A, B and O in the saliva, since in almost one third of those examined, the inhibition tests were negative. The ability to secrete the antigens in the saliva is inherited as a simple mendelian dominant, as shown by studies of

50 families with 149 children, with the gene for the secreting type dominant over the gene for the nonsecreting type. The possible application of this new mendelian trait in medicolegal cases involving the question of paternity is discussed.

ALEXANDER S. WIENER.

THE SPECIFIC CHEMICOREACTIVE POSSIBILITIES OF TISSUE. BRUNO KISCH, München. med. Wchnschr. **79**:1947, 1932.

Simple chemical compounds specifically affect the respiration and the metabolism of different tissues of the body. The effects of fiftieth-molar and hundredth-molar solutions of alanine, serine, methylglyoxal, lactic acid and pyroracemic acid at 37 C. and in nutrient phosphate-free solution of p_H 7.4 on the respiration of the kidney, liver, diaphragm muscle, heart ventricle, retina and Jensen sarcoma tissues of the rat, guinea-pig, rabbit, cat, dog, cow, ox and pig are summarized in tabulated form. Respiration of the kidney is increased by alanine, that of the heart by pyroracemic acid and that of the retina by pyroracemic and lactic acids. Substances that increase the respiration of normal tissues have little effect on the respiration of tumor tissue.

The influences of these simple compounds should be studied from the pathologic and pharamacologic point of view, since they may be as important as the hormonal regulation of the tissue functions.

D. O. ROSBASH.

SYSTEMIC MESENCHYMATOUS EXHAUSTION: A NEW CONCEPTION OF OSTEOGENESIS IMPERFECTA. ERNST JECKELN, Virchows Arch. f. path. Anat. **280**:351, 1931.

In a new-born infant with osteogenesis imperfecta, the connective tissue in general was unchanged, there were areas of normal laminated bone and the resting cartilage was normal. In the regions of enchondral ossification and in the developing teeth, however, there were characteristic changes. These point to a primary inferiority of the mesenchyma, with beginning normal development, followed by an exhaustion of the bone-building mesenchyma leading to imperfect osteogenesis. This opinion differs from that of Bauer, who concluded that in this condition there is a primary congenital dysfunction or anomaly of the mesenchyma.

PERRY J. MELNICK.

INFLUENCE OF OBSTRUCTIVE JAUNDICE ON GASTRIC MOTILITY AND SECRETION. A. W. SELESNJEW, Virchows Arch. f. path. Anat. **280**:405, 1931.

An esophageal fistula and a gastrostomy were produced in four dogs; in three of these the common bile duct was ligated. Feeding experiments resulted in the following data: In the jaundiced dogs motility in general was not altered, although there was some retention after forty-eight hours. There was a gastric juice of very high acidity with much mucus. Individual differences, the mode of administration (whether by mouth or directly into the stomach) and the type of food produced some variations in the results. Ligation of the common duct produced marked widening of the bile ducts and a biliary cirrhosis of the liver.

PERRY J. MELNICK.

RELATIONSHIPS BETWEEN THE PANCREAS AND THE SEX GLANDS. R. BELKIN, I. MICHALOWSKY and L. FALIN, Virchows Arch. f. path. Anat. **280**:414, 1931.

In four cocks from which the pancreas and duodenum had been extirpated, the testes underwent severe atrophy and degenerative changes. These changes are not related to the general loss of weight which occurred, being out of proportion to it (normal, from 1:98 to 1:60; following pancreatectomy, from 1:232 to 1:298). They are not related to the hyperglycemia, because in animals made

hyperglycemic no testicular atrophy occurred. Injections of insulin in normal birds also produced severe loss of weight and testicular degeneration. A hormonal relationship is believed to exist between the pancreas and the sex glands.

PERRY J. MELNICK.

ORIGIN OF INFLAMMATORY TISSUE IN ACTINIA. E. MALOWITSCHKO, Virchows Arch. f. path. Anat. **280**:476, 1931.

To study inflammation in animals without a vascular system, Actinia, a species of Coelenterate, was selected. There are normally an ectoderm, an entoderm and a mesoglia derived from both in which are eosinophils, ameboid cells and fibrocytes. Silk threads were sewed into these animals, and microscopic studies were made on material fixed from a half-hour to seventy days later. The reactions were very similar to those in higher animals. At first, eosinophilic cells phagocytosed the destroyed tissue and disintegrated. Later ameboid cells attacked the silk fibers, even forming syncytial masses around them. Finally after seventy days the foreign material was surrounded by a capsule of collagen fibers.

PERRY J. MELNICK.

SITE OF DEPOSITION OF COAL DUST IN NORMAL AND PATHOLOGIC LYMPH NODES, WITH EXPERIMENTAL STUDIES OF THE RESORPTIVE POWERS OF LYMPH NODES. J. WÄTJEN and W. EILERS, Virchows Arch. f. path. Anat. **280**:487, 1931.

The site of storage of coal dust was studied in autopsy material. Also normal and infected chickens were given injections of india ink, and the carbon storage in the lymph nodes was studied. The site and amount of storage was found to depend on several factors: the amount of carbon, the length of time after the injection, the location of the lymph node, whether peripheral or central to the point of entrance, the state of activation of the reticulo-endothelium and the previous sclerosis of the reticulum. In general, in both peripheral and central nodes the endothelium of the sinuses was found to be the first site of deposition. The storage was greater and of longer duration if the lymph node was activated by an infection. The carbon is then transferred to the reticulum. After sufficient time all of it is in the reticulum unless previous fibrosis makes this impossible. These results differ from Nordmann's conclusion that in peripheral lymph nodes the reticulum is the primary site of deposition.

PERRY J. MELNICK.

EXPERIMENTAL HEMATOGENOUS TONSILLITIS. C. KRAUSPE, Virchows Arch. f. path. Anat. **285**:400, 1932.

By the injection of staphylococci and streptococci into the carotid artery of rabbits and cats, an acute, diffuse inflammation of the tonsils was set up. This reaction was often as superficial as that of the spontaneous necrotizing tonsillitis of rabbits, which is due to infection from the surface of the tonsil. When rabbits were sensitized by repeated injections of streptococci subcutaneously, injection of the same strain into the carotid artery caused lesions that were more circumscribed than those caused by the same organism in nonsensitized animals. Such lesions consisted chiefly of histiocytes. Similar small granulomatous lesions were seen also in the tongue, myocardium and kidney. The injection into the carotid artery of bacteria-free, toxin-containing filtrates of streptococci caused inflammatory changes in the tonsils.

O. T. SCHULTZ.

INCIDENCE OF DISEASE IN JAVA. A. E. SITSEN, Virchows Arch. f. path. Anat. **285**:506, 1932.

This contribution to geographic pathology, which cannot always be sharply delimited from racial pathologic or pathologic anthropology, is based on 3,198 necropsies, of which 173 were done at Batavia and 3,025 at Surabaya, during the

years 1909 to 1927. These data are compared with those derived from the necropsies at Innsbruck in the years 1926 to 1930. In the Java series most of those who came to necropsy were Malays. Exact comparison between the two series of data, even excluding the racial factor, is not possible because of differences in the age groups represented in the two series of necropsies and because of incomplete vital statistics in Java. To mitigate these factors as much as possible the mathematical principles involved are discussed, and a formula is worked out for comparing the actual incidence in the Java series with the expected incidence on the basis of the Innsbruck data. In the Java series the actual percentages of some of the more important diseases were: pneumonia, 33; tuberculosis, 23, and intestinal amebiasis, 8 per cent; circulatory diseases, renal disease and hepatic cirrhosis ranked fifth in point of frequency, with 4 per cent each. Malignant tumors and syphilis each made up 2.5 per cent of the total. The figures for the diseases more characteristic of tropical or subtropical regions, exclusive of intestinal amebiasis were: beri-beri and malaria, each 2 per cent; ankylostomiasis and tropical abscess of the liver, each 1 per cent.

O. T. SCHULTZ.

FUNCTION OF THE RENAL TUBULES. G. EKEHORN, Virchows Arch. f. path. Anat. **285**:605, 1932.

In previous articles of a series devoted to renal physiology, various problems have been discussed, analyzed and summarized. In the last preceding article the conclusion was reached that the glomerular liquid is an ultrafiltrate, which is much more dilute than urine and is formed in much larger quantity. In this contribution, apparently the last of the series, the function of the renal tubules is discussed. All the articles of the series have been based on the author's "On the Principles of Renal Function," published in 1931 as supplement 36 to *Acta medica Scandinavica*. The author concludes that in the kidney with normally functioning glomeruli the tubules secrete or excrete none of the urinary constituents that are preformed in the plasma. The function of the tubules is resorption of the glomerular filtrate. Only creatinine and perhaps sulphates are not resorbed. The resorbed material contains not only water and preformed plasma substances that appear in the final urine, but diffusible substances that do not appear in the bladder urine. The resorbed material varies in quantity and composition under varying conditions. Resorption by the renal tubules is a vital process that is regulated by hormones, ions and perhaps excretable substances of the plasma.

O. T. SCHULTZ.

RESISTANCE OF MEGAKARYOCYTES TO EXPERIMENTAL CONDITIONS. P. W. SSIPOWSKY, Virchows Arch. f. path. Anat. **285**:723, 1932.

Fully grown rabbits were subjected to a variety of procedures to determine the resistance of the megakaryocytes of the bone marrow of the femur to the procedures used. The latter were ligation of the veins to produce stasis, ligation of the artery to cause local anemia, application of heat and cold, production of an acute infection and the use of hemolytic substances. To all these procedures the megakaryocytes were less resistant than the other elements of the marrow. The changes were degenerative: pyknosis, karyorrhexis and plasmorrhexis. Marked pyknosis of the megakaryocytes was evident before any changes could be seen in any of the other cells. Reestablishment of the circulation after ligation of the vein was followed by a return of the megakaryocytes to normal.

O. T. SCHULTZ.

EFFECT OF SECTION OF BOTH VAGI ON THE STOMACH. J. M. LASOWSKY and A. N. PTSCHELINA, Virchows Arch. f. path. Anat. **285**:755, 1932.

In the dog, section of both vagi above the diaphragm was not followed by the formation of erosions or ulcers of the stomach. Secretion of mucus by the mucous

cells was increased, and some of the chief cells contained mucus. The secretory granules disappeared. These alterations are similar to those of chronic gastritis, and are therefore not characteristic of the latter condition.

O. T. SCHULTZ.

GENERALIZED TROPHIC DISTURBANCES FOLLOWING EXPERIMENTAL INJURY TO THE DENTAL NERVES. P. N. KARTASCHOW and L. M. MATWEEWA, Virchows Arch. f. path. Anat. **286**:11, 1932.

In dogs, the pulp cavity of one or two teeth was exposed. A small quantity of croton oil or arsenic paste was introduced into the pulp, after which the opening into the tooth was sealed with cement. The animals appeared well after the dental operation. But two or more months later their appetite failed, they lost weight, the hair fell out and the animals died as the result of acute gastro-enteritis. These disturbances developed more quickly in young dogs than in older ones, and in both young and older animals the advent of serious symptoms was hastened by repeated spinal tappings. The authors interpret the symptoms as trophic disturbances. Chemical trauma to the dental nerves leads to reactive changes in the central nervous system. The latter may be of such a character and grade that the symptoms resemble those of encephalitis. Recovery from an encephalitic attack may be followed by recurrence. Disturbances of nervous regulation, due to central nervous system changes, lead to alterations of the physicochemical balance of the organs.

O. T. SCHULTZ.

EXPERIMENTAL SCLERODERMA DUE TO PARATHYROID HORMONE. H. SELYE, Virchows Arch. f. path. Anat. **286**:91, 1932.

The author gives a concise review of the history, clinical manifestations, pathology and theories of scleroderma in human beings. In his own experimental work, which was done in the school of hygiene of the Johns Hopkins University, nursling rats from 7 to 14 days old received a daily intraperitoneal injection of from 5 to 10 units of parathyroid extract-Collip for three or four successive days. In 20 per cent of the animals changes occurred that the author considers identical with those of scleroderma in human beings. These changes began after the second dose of the parathyroid extract, the early changes being similar to those of the edematous stage of scleroderma. Then followed an indurative stage, and the atrophic stage was reached in about fifteen days. Animals that received only a single course of three or four daily injections recovered, and two months after the first administration the skin had returned to normal. The author thinks that hyperparathyrosis is not a disease entity, but that there are several forms of hyperparathyrosis characterized by different clinical and pathologic states. An excess of parathyroid hormone brings about a condition of the body that manifests itself in a variety of disease pictures. Among these he includes scleroderma, osteitis fibrosa cystica and Albers-Schoenberg marble disease of bone. In a number of other syndromes, Paget's disease of the bone, von Recklinghausen's neurofibromatosis, progressive hemiatrophy of the face and periarteritis nodosa, in which parathyroid hyperactivity has been postulated, the relationship of hormone and disease is not so clear. The article, which is not unduly long, contains 191 references to the literature.

O. T. SCHULTZ.

FUNCTIONS OF THE RETICULO-ENDOTHELIAL SYSTEM. R. FREUND, Virchows Arch. f. path. Anat. **286**:526, 1932.

With a gold sol, Freund found it possible to obtain much more uniform vital storage by the reticulo-endothelial cells than with substances previously used. Treatment of the animals with an electrocolloidal copper solution inhibits the vital storage of gold for forty-eight hours. Vital storage of gold after copper treatment was used by the author as an indicator in a variety of experiments planned to study the functional activities of the active mesenchyme. It was not possible to

influence antibody (hemolysin) formation, anaphylaxis or the chemotherapeutic response in experimental mouse trypanosomiasis. A variety of pharmacologic substances, such as the hormones, calcium, potassium, histamine and caffeine, yielded different vital storage pictures, depending on the effect of the substance used on the circulation of the organ. The reticulo-endothelial system has a variety of functions which may be influenced separately and each of which may therefore be looked on as a partial function of the cell. In the regulation of these functions, the blood stream is the underlying factor. It influences function by its composition, by the physicochemical properties of its contained substances and most of all by its rate of flow through the organs.

O. T. SCHULTZ.

DEPOSITION OF CHOLESTEROL IN THE LUNGS AFTER INTRAVENOUS INJECTION. G. A. MERKULOW, Virchows Arch. f. path. Anat. **286**:571, 1932.

A finely dispersed colloidal preparation of cholesterol in dextrose or levulose solution was injected intravenously into animals, chiefly rabbits. The cholesterol content of the preparation varied from 3 to 20 per cent and the quantity of solution injected from 5 to 32 cc. Single or repeated injections were made, and the animals were killed at intervals of from twenty minutes to twenty-five days after injection. The deposition of cholesterol in finely particulate form in the capillaries of the lung began almost immediately after injection and continued for several days, the particles becoming larger. Esterification of the cholesterol began on the fifth day after injection. After repeated injections the cholesterol deposit assumed a crystalline form. After the longer intervals and after repeated injections, intimal proliferation occurred in the vessels in which cholesterol had been deposited. The injection and the early deposition were followed by the accumulation of leukocytes in the capillaries of the lung and by transient peripheral leukocytosis. The latter was followed by leukocytic infiltration along the arteries of the lung. The levulose cholesterol sol often caused diffuse thrombosis of the small vessels of the lung.

O. T. SCHULTZ.

Pathologic Anatomy

CALCIFIED PULMONARY MILIARY TUBERCULOSIS. BARNET P. STIVELMAN, Am. Rev. Tuberc. **26**:437, 1932.

Chronic miliary tuberculosis of the lungs is of rare occurrence being observed 4 times in over 8,500 tuberculous patients who were subjected to thorough physical and roentgenographic examinations. Among the early reports is that of Wunderlich in 1860. Longcope described 6 cases in 1906, and Northrup in 1914 was probably the first to show roentgenologic evidence of chronic miliary tuberculosis of the lungs in a boy of 6 years. Since then reports have increased. The disease is of more than academic interest, and is not necessarily of the gravest prognostic import when involving a part of or an entire lobe of the lung. On the other hand, miliary involvement of both lung fields almost invariably evokes a fatal prognosis. The author presents a bilateral case with roentgenogram in a Negress, 31 years of age, and discusses the differential diagnosis from broncholithiasis and miliary carcinomatosis.

H. J. CORPER.

MASSIVE ATELECTASIS COMPLICATING PULMONARY TUBERCULOSIS. LOUIS I. SOKOL, Am. Rev. Tuberc. **26**:442, 1932.

A boiling down of the various definitions presented in the literature yields the following conception, which may be considered applicable to all types of massive atelectasis; an acute or subacute febrile complication, produced by the obstruction of a bronchus and followed by a more or less complete absorption of vesicular air in the corresponding portion of the lungs, thus giving to the organ a structure resembling the fetal lung. It is characterized by the clinical symptoms of unilateral

pulmonary consolidation, with displacement of the mediastinum and its contents toward the affected side. Massive atelectasis was known as long ago as 1844, when it was first reported by Legendre and Bailey. Etiologic causes may be (1) intrabronchial, (2) extrabronchial and (3) idiopathic. Two cases are reported by the author: (1) one of extrabronchial origin, caused by a fibrous strand, and (2) the other intrabronchial, caused by plugging by a blood-clot or cast. Atelectasis must be differentiated from pneumonia, spontaneous collapse and pleurisy with effusion, as well as from acute dilatation of the heart, infarction, diaphragmatic hernia, pulmonary embolus and thrombosis.

H. J. CORPER.

PATHOLOGIC PECULIARITIES OF TUBERCULOSIS IN THE AMERICAN NEGRO. MAX PINNER and JOSEPH A. CASPER, Am. Rev. Tuberc. **26**:463, 1932.

The postmortem findings in 303 Negroes and 219 white patients who died of tuberculosis are compared. The differences noted were a greater frequency of miliary tuberculosis in the Negro (37.3 per cent as compared with 15.5 per cent of the white patients), a greater frequency of hematogenous metastases in the Negro (84.2 per cent to 40 per cent), a greater frequency of lymphatic metastases in the Negro (66.8 per cent to 10.8 per cent) and various qualitative differences in the pattern of the tuberculous lesions. Infection tends to produce a high state of allergy in the Negro, but he does not readily acquire a state of increased resistance coincidentally. Lack of infection in childhood does not exist in the Negro. The authors believe a true genotypic difference exists between the Negro and white races, accounting for their different reaction to tuberculosis.

H. J. CORPER.

PATHOGENESIS OF THE CHANGES IN THE CEREBROSPINAL FLUID IN MENINGITIS. FRANK FREMONT-SMITH, Arch. Neurol. & Psychiat. **28**:778, 1932.

The author defines meningitis as an infection of the cerebrospinal fluid which largely originates "in the arterial blood in the capillaries of the choroid plexuses" and probably also comes from "other sources." Fremont-Smith likens the cerebrospinal fluid in meningitis to an abscess. In meningitis the pressure of the cerebrospinal fluid is increased, as are the cell and protein contents. The contents of sugar and chlorides are in contrast decreased, but a quantitative relationship between the increase in protein and the decrease in chlorides is most likely due to the decrease of chlorides in the plasma of the blood. On the whole, the chemical composition of the cerebrospinal fluid in meningitis depends chiefly on the composition of the blood plasma.

G. B. HASSIN.

HISTOLOGIC STUDIES IN MENINGITIS. GEORGE B. HASSIN, Arch. Neurol. & Psychiat. **28**:789, 1932.

The four commonest types of meningitis (purulent, cerebrospinal, tuberculous and pneumococcic) are described in detail with reference to the cell changes in the subarachnoid space and the condition of the perineurial and endoneurial prolongations of the meningeal spaces and cerebral parenchyma. Perineuritis is always present more or less, and affects the subarachnoid spaces and the parenchyma of the brain as well, causing rarefaction, hydrocephalus and edema. The mesothelial cells exhibit, with other meningeal cells normally present in the subarachnoid space, a marked meningitic reaction but no phagocytic activities. They exhibited a reaction in a case of an acute mental disorder. It was similar to that produced experimentally by a subarachnoid injection of laked blood, lampblack and similar products, and is generally designated aseptic meningitis. Such a type of meningitis in a mental disorder should be considered the result of the action of chemical substances discharged by the brain into the subarachnoid space.

AUTHOR'S ABSTRACT.

So-Called Nonsuppurative Encephalitis and Encephalomyelitis. Joseph H. Globus, Arch. Neurol. & Psychiat. **28**:810, 1932.

Globus would restrict the term encephalitis to inflammatory conditions of the brain caused by an infectious agent. He gives a brief review of the histologic changes in various forms of encephalitis, and admits that it is not possible to differentiate them on "geographic and cytologic grounds." The cerebral changes produced by toxins or inorganic poison, such as lead, should not be classified, says Globus, as encephalitis, for morphologic manifestations of inflammatory disease process are absent.

G. B. Hassin.

The Brain in Acute Rheumatic Fever. N. W. Winkelman and John L. Eckel, Arch. Neurol. & Psychiat. **28**:844, 1932.

The brain is among the organs which are usually involved in rheumatic fever, permanent cerebral manifestations usually depending on an endocardial condition. As a rule, however, the changes in the brain are transient. The clinical picture may be dominated by choreic movements or may resemble that of lethargic encephalitis.

The authors studied five cases, and consider the changes to be similar to those present in any general infection; that is, they are not specific. In one of their cases the changes were probably due to cerebral emboli that resulted from loosening of the small particles of the cardiac valves. The brain changes were not due to hyperpyrexia and were present also in the parenchyma (cloudy swelling) and in the mesodermal tissues, of which the most significant were the so-called productive endarteritis of the small blood vessels and edema of the brain. Real inflammatory phenomena were lacking; in some cases so-called acellular cortical areas of destruction were in evidence.

G. B. Hassin.

Nerve Degeneration in Poliomyelitis. W. P. Covell, Arch. Neurol. & Psychiat. **28**:1056, 1932.

The site of the functional loss in poliomyelitis, produced experimentally in monkeys, is in the ganglion cells of the anterior horns or at their synapses with the upper motor neuron. The duration of the paralysis in Covell's experiments was not more than forty-eight hours. The extent of the injury to the cells was studied in the lower cervical, dorsal and lower lumbar regions of the spinal cord. The greatest number of ganglion cells destroyed was in the intermediate, dorsolateral and ventrolateral groups of the spinal cord, and more than half of the cells were destroyed in the first twenty-four hours of paralysis. After twelve hours of paralysis, the ganglion cells exhibited marked polymorphonuclear cell neuronophagia (63.6 per cent of the neuronophages were polymorphonuclear leukocytes), which progressively decreased, being only 24.3 per cent after thirty-six hours; the remaining cells were other phagocytes. The degree of damage to the ganglion cells as well as to the spinal roots and peripheral nerve fibers was also studied by means of intravenous injections of neutral red dye. It stains deeper the parts that are destroyed, the ventral horn cells and the ventral roots of the spinal cord. In early stages, it becomes clumped to one side of the nucleus of the damaged ganglion cell; in the later stages it shows in the cytoplasm as minute globules.

G. B. Hassin.

Encephalitis Disseminata. James C. Gill and Richard Richter, Arch. Neurol. & Psychiat. **28**:1072, 1932.

In a man, aged 23, a right-sided hemiparesis suddenly developed with ipsilateral ptosis and facial paresis. About eleven months later a weakness appeared on the left side, while that of the right side disappeared, and a paralysis of the right

facial nerve developed. The patient was lethargic, and swallowed with difficulty. Serologic and other findings were negative; the blood picture was normal, but the temperature became elevated shortly before death, which occurred one month after the onset of the second attack.

Necropsy revealed numerous foci of softening in the white substance, especially in the right hemisphere; microscopically, foci of demyelinization were present, which contained masses of fat granule bodies in many instances. Other changes were in the axons, with numerous astrocytes and a marked increase of neuroglia fibers at the edge of the focus. The cortex and basal ganglions were not involved. The blood vessels showed infiltration with gitter cells mixed with lymphocytes and plasma cells; no foci of softening were present in the basal ganglions, pons or cerebellum, but a lymphocytic infiltration was sometimes marked. In short, multiple degenerative softening was microscopically associated with inflammatory phenomena in the brain stem, which the authors consider not secondary to the massive degenerative phenomena, but independent. The authors evidently had great difficulty in classifying their case. It looked to them like disseminated encephalomyelitis, multiple sclerosis and Schilder's disease, which they would all include in the group of nonsuppurative infectious encephalomyelitis.

G. B. HASSIN.

THE NONSPECIFICITY OF THE HISTOLOGIC LESIONS OF DEMENTIA PARALYTICA. FREDERIC WERTHAM, Arch. Neurol. & Psychiat. **28**:1117, 1932.

Chickens were inoculated with Spirochaeta gallinarum and their central nervous system studied by Wertham histologically. The sections, embedded in celloidin, measured 12 microns. The meninges, especially the cerebral, were in some cases slightly infiltrated with lymphocytes and plasma cells. Ganglion cell changes were more or less in evidence (shrinkage and pyknosis, so-called severe cellular disease and cellular vacuolation). The vessels showed hyperemia, and in the smaller blood vessels there was frequently an adventitial infiltration with plasma cells and large amounts of iron. The glia exhibited proliferation in the form of small clusters, which were frequent in the cerebellum, medulla and forebrain. There were numerous Hortega cells (called Hortega glia by Wertham) in the form of sausage cells, and they often contained iron. In nature and distribution, this corresponded to the iron found in dementia paralytica, for which it is generally considered specific and called dementia paralytica iron. In the spinal cord there were glia clusters in the dorsal columns and also small foci of demyelinization (probably artefacts). However, the foregoing histologic features (plasma cell infiltration, proliferation of Hortega cells and the presence of dementia paralytica iron) were also found in a number of control chickens; that is, a picture closely resembling that of dementia paralytica in man and spirochetosis gallinarum may be a spontaneous disease in chickens, and need not cause any clinical symptoms.

G. B. HASSIN.

TORSION OF THE OMENTUM. J. H. MORRIS, Arch. Surg. **24**:40, 1932.

Morris reviews the literature and adds 3 personally observed cases, to bring the total reported to 217. Torsion of the omentum occurs on its long axis and may be acute, with complete infarction, or recur as a result of incomplete rotation. Preoperative diagnosis is rare, less than 8 per cent of the cases having been correctly diagnosed. A frequent initiating factor is the fixation of the free end of the omentum to an inflammatory focus or to an operative scar. The torsion therefore may be classified as unipolar when the lower end is free and bipolar when the lower end is fixed. The most frequent associated lesion is hernia. In cases not associated with hernia, cysts, tumors and regional inflammatory processes are to be considered as contributing etiologic factors. The changes are congestion, edema, thrombosis, hemorrhagic infarction and necrosis.

N. ENZER.

CONGENITAL CYSTIC DILATATION OF THE COMMON BILE DUCT. M. M. ZINNINGER and J. R. CASH, Arch. Surg. **24**:77, 1932.

The authors report at length a case of cystic dilatation of the common bile duct in which the cyst was about 10 cm. in diameter. It was lined by well preserved mucosa, similar in structure to gallbladder mucosa. The cystic duct emptied into the cyst, and the cyst in turn emptied into the duodenum by a duct joined just before its terminal end by the pancreatic duct. Eighty-two cases were discovered in the literature, and these are reviewed in detail. The theories presented indicate that this condition is generally recorded as a congenital anomaly, although there is some belief that it is idiopathic in formation.

N. ENZER.

TRAUMATIC NECROSIS OF THE LIVER WITH EXTENSIVE RETENTION OF CREATININE AND HIGH-GRADE NEPHROSIS. F. C. HELWIG and T. J. ORR, Arch. Surg. **24**:136, 1932.

In a young boy severe traumatic necrosis of the liver developed as the result of an automobile injury, and he died on the eleventh day of illness. The nonprotein nitrogen of the blood rose to 240 mg. per hundred cubic centimeters and the creatinine of the blood to 25 mg. Necropsy revealed intraperitoneal hemorrhage, a large, swollen, pulpy liver and greatly swollen, hyperemic kidneys. Microscopic examination revealed areas of necrosis and hemorrhage in the liver with some evidence of an acute inflammatory reaction and extensive parenchymatous degeneration of the cortex and tubules of the kidney. There was no evidence of fatty degeneration in the kidney. The authors were able to find only one other case in the literature, reported in 1927, by Furtwaengler. In this case bilateral necrosis of the renal cortices occurred. The authors believe that the renal damage was the result of a toxin, elaborated in the areas of hemorrhagic necrosis in the liver.

N. ENZER.

THE SPLENIC LESION IN HEMOLYTIC JAUNDICE. WILLIAM P. THOMPSON, Bull. Johns Hopkins Hosp. **51**:365, 1932.

Hemolytic jaundice is a clinical and pathologic entity which exhibits typical splenic changes. In a study of thirty such spleens enlargement was noted on gross examination (average weight, from 1,000 to 1,500 Gm.). On microscopic study the venous sinuses were enlarged and frequently empty. The sinus endothelium, bulging into the sinus lumen, was hypertrophied. The malpighian bodies were small and widely scattered. The pulp, which presented the most characteristic feature of the microscopic appearance, was a mass of closely packed red cells. There was no increase in the connective tissue or the iron pigment. In short, the splenic changes in this condition are so typical that the diagnosis of hemolytic jaundice is readily made on the finding of dilated venous sinuses, prominent sinus endothelium, small, scattered malpighian follicles and pulp densely packed with erythrocytes.

E. KLEIN.

SO-CALLED ATYPICAL LYMPHOGRANULOMATOSIS. C. STERNBERG, Beitr. z. path. Anat. u. z. allg. Path. **87**:257, 1931.

The author preliminarily reviews the characteristic histology of lymphogranulomatosis and emphasizes that in the absence of the characteristic giant cells the diagnosis is unjustified. There are instances in which the cells are so large and atypical as to occasion the suspicion of sarcoma. But even here there is definite polycellularity, a tendency to fibrosis and necrobiosis. The possibility of a transition to sarcoma in such cases is denied by the author. He further cautions that the diagnosis of lymphogranulomatosis is at present a histologic one and should never be confused with the term atypical.

W. S. BOIKAN.

THE PLASMA CELL REACTION OF THE SPLEEN, ESPECIALLY IN CARCINOMA. I. MÜLLER, Centralbl. f. allg. Path. u. path. Anat. **55**:180, 1932.

This author investigated the plasma cell reaction of fifty-four spleens, twenty-five of which were obtained from bodies in which carcinoma occurred. The number of plasma cells in the spleen was unrelated to the number, size or situation of carcinomatous metastases in the body. The plasma cell reaction was most marked when the tumors were necrotic, so considerable quantities of protein came into the circulation before death. Some spleens had a very slight reaction where the tumor had been removed by operation. In spleens from persons who had died of caseous pulmonary tuberculosis there was a rich plasma cell reaction, whereas it was absent in the spleens of people who had died of trauma or chronic heart disease. The explanation of this reaction is found in the filtering activity of the spleen called forth by protein, from the aforementioned lesions, in the blood. In carcinoma, formed cellular elements call forth this reaction after disintegration. This reaction may explain the well known immunity of the spleen to tumor.

GEORGE RUKSTINAT.

CYSTIC DILATION OF THE PERITONEAL LYMPH VESSELS IN TUBERCULOSIS. E. SIEDECKI, Centralbl. f. allg. Path. u. path. Anat. **55**:183, 1932.

In the body of a 22 year old woman who died of pulmonary laryngeal, bronchial and intestinal tuberculosis long-stalked cysts were found pendant from the small bowel serosa in the region of mucosal ulcers. The largest cyst, 13.7 cm. long, 1 cm. across at the base and 3 cm. at its bulbous end, was at the junction of the jejunum and ileum, and two others were respectively 30 and 50 cm. distal to it. Microscopically these cysts were dilated lymph channels the efferent patch of which had been obstructed by tubercle formation and inflammation in the region of an ulcer. Presumably the inflow of lymph was not impaired, and the cysts resulted. The name "lymphangiectasiae cysticae peritonaei" is suggested for such structures.

GEORGE RUKSTINAT.

A SUPRARENAL GLAND STONE. E. PETRI, Centralbl. f. allg. Path. u. path. Anat. **55**:292, 1932.

In the body of a 54 year old man, who had suffered from cardiac decompensation and who died of empyema of the pleura, the left suprarenal gland was about one third the usual size. Its medulla was occupied by a date pit-sized stone, yellowish-gray and somewhat crumbly. On analysis the stone was found to contain 4.7 per cent of calcium, principally calcium phosphate, 7 per cent cholesterol and traces of iron. The cortex of the gland was poor in lipoid, compressed but still recognizable. In addition to the stone the medulla contained only thick collagenic connective tissue masses, in the inner layers of which were calcium rests and slits from dissolved cholesterol. Petri suggests that a primary closure of the medullary veins followed by total necrosis of the medulla may have preceded the stone formation. He cites the chronic cardiac ailment as a basis for the formation of marantic thrombi and the compatibility of such a unilateral lesion with life.

GEORGE RUKSTINAT.

PERITONITIS ORIGINATING IN INTESTINAL ENDOMETRIOSIS AS A COMPLICATION OF PREGNANCY. F. HAUFLER, Virchows Arch. f. path. Anat. **280**:822, 1931.

A woman, aged 30, had acute intestinal symptoms that led to a diagnosis of acute appendicitis in the sixth month of her first pregnancy. At operation generalized peritonitis was discovered. On the serous surface of a loop of small intestine were found a number of small abscesses, to which the peritonitis was ascribed. A portion of intestine 17 cm. long was resected. Gross examination of this revealed a number of small, firm, subserous nodules, as well as several small

abscesses. The mucosa appeared normal. On microscopic examination the nodules were found to be composed of endometrial tissue. The epithelium of the glands had undergone the changes of the endometrial glands during pregnancy, and the surrounding stroma had been transformed into decidua. At one point microscopic examination revealed a communication between a narrow cleft of the mucosa and a gland of an endometrial nodule. The lumen of this passage was filled with leukocytes. The involved intestine came from the jejunum. The author is convinced that a communication existed between the lumen of the intestine and the endometrioid glands, and that infection occurred when the endometrioid tissue underwent the changes of pregnancy.

O. T. SCHULTZ.

ARE LOCALIZED APICAL THICKENINGS OF THE PLEURA TUBERCULOUS IN ORIGIN? A. BESSIN, Virchows Arch. f. path. Anat. **280**:837, 1931.

Many observers look on the localized, cartilage-like areas of thickening of the pleura that are seen so frequently, especially in elderly persons, at or just below the apex of the lung, as the scars of a healed tuberculous infection. In order to determine whether such lesions are tuberculous in origin, Bessin examined a series of them histologically and injected the ground material into guinea-pigs. The material selected for study came from twenty-seven cases in which at necropsy there was no macroscopic evidence of tuberculosis. In none of the twenty-seven cases did the pleural scar reveal any histologic evidence of tuberculosis. In only two instances did tuberculosis develop in the inoculated animal. The author concludes that in the great majority of cases localized apical thickening of the pleura is due not to tuberculosis but to mechanical factors.

O. T. SCHULTZ.

CONGENITAL SYPHILIS OF THE INTESTINE. D. Y. KU, Virchows Arch. f. path. Anat. **280**:852, 1931.

Ku reports four cases of congenital syphilis with syphilitic involvement of the small intestine. He describes three histopathologic types of lesion. In one the mucosa was atrophic and was replaced by granulation tissue. Miliary syphilomas were present in the muscle coat. In a second case there was diffuse thickening of the wall owing to proliferation of the connective tissue of the mucosa and submucosa. In a third form, necrotic gummatous lesions of the mucosa and submucosa were associated with ulcers. Spirochetes were found in the tissues of the intestinal lesions in two of the cases.

O. T. SCHULTZ.

VARIATIONS IN THE SHAPE OF THE NUCLEUS PULPOSUS OF THE INTERVERTEBRAL DISKS. R. BÖHMIG, Virchows Arch. f. path. Anat. **280**:873, 1931.

In a previously published study of the vertebral column from its early embryonic development to the completion of development of the vertebral bodies during the early part of the third decade of life, the author described variations in the form of the nucleus pulposus that he held to be developmental in origin. Such bottle-shaped and double V-shaped nuclei he believed to be the result of the growth of the tissue of the nucleus into the canal of the primitive notochord. Schmorl considered such variant forms of the nucleus pulposus and the downgrowth of cartilaginous nodules from the disk into the spongy bone of the body, when they occur in older persons, to be pathologic in origin and to be due to microfractures of bony trabeculae and other mechanical damages. Böhmig now describes nucleus identical with those seen in the earlier periods of life. Contrary to Schmorl's belief, he holds that these also are developmental in origin. Segmentation of the nucleus into two or more round or oval masses separated by fibrous tissue or fibrocartilage also occurs both before and after the age of 30 and is developmental in nature and not pathologic.

O. T. SCHULTZ.

TWO CASES OF PRIAPISM. S. SCHEIDEGGER, Virchows Arch. f. path. Anat. **283**: 178, 1932.

The condition in each case began a few days before death and persisted after death. The onset was preceded in each case by an infection of the upper part of the respiratory tract. In the first patient, aged 62, there were found at necropsy an early polypoid carcinoma of the rectum and thrombosis of the pelvic venous plexus. The blood sinuses of the corpora cavernosa were distended by recently thrombosed blood, in which no tumor cells were found. The sinuses of the corpus spongiosum were empty. The second patient, aged 28, had taken a yohimbine preparation at irregular intervals, the last time a few days before the onset of priapism; this was ushered in with subcutaneous hemorrhages of the thighs, scrotum and penis. Necropsy revealed widespread, partly purulent thrombosis of the pelvic veins and distention of the sinuses of the corpus spongiosum by blood that was still liquid after death. The corpora cavernosa were empty. The walls of the smaller pelvic vessels were necrotic. The second case is interpreted as a septic thrombosis of the pelvic veins occurring in the course of a generalized infection, the localization of the process in the pelvic vessels being the result of dilatation of the vessels brought about by the action of yohimbine.

O. T. SCHULTZ.

INTRAVASCULAR PRESSURE AS THE CAUSE OF ARTERIOSCLEROSIS. E. MOSCHCOWITZ, Virchows Arch. f. path. Anat. **283**:282, 1932.

Fifty necropsies that revealed arteriosclerosis of the pulmonary artery and its branches are analyzed and the findings discussed in relation to the author's thesis that intravascular pressure, normal or increased, is the essential factor in the pathogenesis of arteriosclerosis. The necropsies were done at the Mount Sinai Hospital, New York, during the years 1926 and 1927, and formed part of a total of 770 necropsies at that hospital during these two years. This material formed the basis of articles previously published (*Am. J. M. Sc.* **174**:388, 1927; **178**:244, 1929) in which, as in the present communication, the author presents the deductions that uphold his thesis.

O. T. SCHULTZ.

CONGENITAL MALDEVELOPMENT OF THE LARYNX. ANNELISE ROHRMANN, Virchows Arch. f. path. Anat. **283**:304, 1932.

The anomaly occurred in a new-born girl with multiple malformations, and consisted in rudimentary development of the epiglottis. In place of the latter was a group of cartilaginous nodules.

O. T. SCHULTZ.

TUBERCULOSIS OF BONE, ESPECIALLY OF THE SKULL. J. ERDHEIM, Virchows Arch. f. path. Anat. **283**:354, 1932.

Erdheim begins his fifty-nine page dissertation with the statement that tuberculosis of bone has not received the careful attention by general pathologists that its importance warrants. He then presents a histologic study of a case of tuberculosis of the skull, building a word picture of the dynamics of the process from beginning to end. In the skull, the course of events can be much more clearly traced than in other bones. In the zone of active progressive involvement, typical miliary and conglomerate tubercles are formed in the marrow spaces. The tuberculous granulation tissue causes lacunar resorption of the bone by pressure. Caseation leads to necrosis of the granulation tissue and of bone that has not been resorbed. The area of earliest destruction, after it breaks through the outer table, leads to the formation of a tuberculous cavity. Peripheral to the advancing zone, the bone undergoes osteosclerosis, characterized by fibrosis of the marrow tissue and by deposition of new bone on the surface of the original trabeculae. This reaction, which Erdheim terms paratuberculous, is due to tuberculotoxic substances

that diffuse out into the tissue. It is seen also in the pericranium and scalp and in the dura, when the tuberculous process approaches these structures. The paratuberculous zone is in turn invaded and eroded by the advancing process. The destructiveness of the latter is greater in the diploe than in the outer table, and it is greater in the inner table than in the diploe, because the process spreads along the outer surface of the dura. Because of the undermining of the outer table by destruction of the diploe and because of the still greater destruction of the inner table, the defect of the inner table is much larger than that of the outer table. Anatomically, this condition is characteristic of tuberculosis of the skull, and its roentgenologic detection should establish the diagnosis. The clinical diagnosis in the case studied was gumma of the skull, and the patient had received antisyphilitic treatment for two years. Erdheim maintains that the correct diagnosis should have been made from the roentgenogram, and states that he made the diagnosis of tuberculosis from the verbal description even before he had seen the specimen. As the process extends peripherally, healing may take place in the wall of the original cavity. The latter may be partly epithelialized by the downgrowth of the epidermis of the scalp; a fibrous connective tissue membrane is formed, and beneath this new bone formation may occur. The new bone may be primitive blue bone, its primitive character being the result of the action of diffusible tuberculotoxin. In the outer table, the osteosclerotic process that precedes destruction leads to smooth thickening of the outer surface; in the inner table, it leads to osteophytic thickening of the inner surface. Spread of the process within the diploe may lead to the formation of secondary cavities that break through the outer table and form sinuses through the scalp. The floor of the original cavity is formed by the thickened dura, the thickening being due to tuberculous pachymeningitis externa and interna. The pia-arachnoid becomes adherent to the internal surface of the dura. Progressive erosion of the dura leads finally to abscess of the brain. The brain lesion may be tuberculous or may be due to secondary invaders of the cavity. Although reparative processes in the older portions of the tuberculous area of the skull may lead to apparent healing, recidivation usually occurs.

O. T. SCHULTZ.

CHOLESTEROL PLEURITIS AND PERICARDITIS. G. DÁNIEL and S. PUDER, Virchows Arch. f. path. Anat. **284**:853, 1932.

A man, aged 52, had contracted syphilis fifteen years before death. Five years before death he had pleuritis, since which time he had been in poor health. Two weeks before death a dry cough, dyspnea and extreme weakness developed. The Wassermann reaction was strongly positive, and a few tubercle bacilli were found in the sputum. The clinical diagnosis lay between gumma and tuberculosis of the left lung. Autopsy revealed a massive chyliform exudate in the pericardial and left pleural cavities and a smaller quantity of similar exudate in the right side of the thoracic cavity. The exudate contained cholesterol, fats and phosphatids. The involved serous membranes were chronically inflamed, the process being histologically nonspecific. The authors ascribe the character of the exudate to inspissation of an originally hemorrhagic purulent exudate. In the upper lobe of the left lung was a fibrous nodular area. Histologically it could not be definitely determined whether this was a gumma or a tuberculoma; the authors think it was a combination of the two processes. There was syphilitic aortitis. In the available literature the authors could find only two previously reported cases of cholesterol pericarditis.

O. T. SCHULTZ.

CONGENITAL FIBROUS MYOCARDITIS. C. FROBOESE, Virchows Arch. f. path. Anat. **284**:861, 1932.

The author gives a brief description and discussion of a case of fibrous myocarditis of the right ventricle in a girl 6 months old. There were no other cardiac abnormalities. He believes that the fibrotic process was the result of

infection, which occurred either in the first few weeks of life or before birth. The child had had an attack of dyspnea shortly after birth. The author inclines to the view that the process had its origin in intra-uterine life.

O. T. SCHULTZ.

ARTERIOLAR CHANGES IN CHRONIC NEPHRITIS. M. A. ZACHARJEWSKAJA. Virchows Arch. f. path. Anat., **284**:890, 1932.

The author reports a histologic study of the arterioles of nineteen kidneys, undertaken for the purpose of determining the relation of arteriolar sclerosis and arteriolar necrosis to each other and to the severity of the nephritic process. The material is subdivided into acute, subacute and chronic glomerulonephritis (eight cases), nephrosis (two cases) and nephrosclerosis (nine cases). Obliterative endarteritis was noted in the arterioles that supplied fibrosed glomeruli. Arteriolar sclerosis was absent or slight in the kidneys in acute and subacute glomerulonephritis. The sclerosis bore no apparent relation to the degree of the inflammatory process present in the kidney. Necrosis of arterioles and glomeruli was not seen alone, but was observed only in association with arteriolar sclerosis, and usually with the more severe grades of the latter.

O. T. SCHULTZ.

Pathologic Chemistry and Physics

THE SPERMICIDAL POWERS OF CHEMICAL CONTRACEPTIVES. J. R. BAKER, J. Hyg. **29**:323, 1930; **31**:189 and 309, 1931; **32**:171 and 550, 1932.

A comparative examination was made of the effectiveness for human and guinea-pig sperms of a large group of pure substances and commercial contraceptive preparations of known chemical composition. The conditions of the examination were so arranged as to approximate as nearly as possible in vitro the conditions and concentrations of the acting substances within the vagina. The killing concentration was determined for a series of pure substances, and it was found that the six having the greatest spermicidal power were quinones. In the hydroxybenzenes and their derivatives, the relative positions of the hydroxyl groups were significant. Of the commercial pessaries tested with human sperms, those which contained butter of cocoa were less effective than those which did not. The effectiveness of foaming mixtures and of soaps is discussed. Human and guinea-pig sperms were susceptible to the substances tested in almost the same degree. Evidence is presented for the existence in human semen of a substance which protects both human and guinea-pig sperms against some spermaticides, especially sodium oleate, vanillin and potassium borotartrate.

L. E. SHINN.

THE COMPOSITION OF THE LIPOIDS IN NORMAL AND PATHOLOGIC ORGANS. B. LUSTIG and E. MANDLER, Biochem. Ztschr. **249**:352 and 366, 1932.

The lipoid content of two normal, two carcinomatous and one melanosarcomatous liver was examined. Two fractions were distinguished, one which could be directly extracted and a second which was obtained after pepsin digestion (bound lipoid). In the carcinoma extracts, the phosphorus content was diminished. In the melanosarcoma extracts, normal values were found. The phosphorus content of the directly extractable carcinoma extracts corresponds with the phosphorus content of the substances precipitable with acetone, while in the melanosarcoma extract, only a part of the phosphorus-containing substances can be precipitated with acetone. The phosphatides precipitated with acetone in the carcinoma and sarcoma extracts show an increased phosphorus content in comparison with that in normal livers. The acid number of the sarcoma extracts was markedly increased, with simultaneous elevation of the ester number. The amount of the nonsaponifiable lipoid and of the cholesterol was increased in the directly extractable lipoids of the

carcinoma and sarcoma extracts, but decreased in the bound lipoid of the melanosarcoma. In the bound lipoid, a decrease of the phosphorus content was observed in carcinoma and sarcoma extracts. The amount of the nonsaponifiable material was increased in the carcinoma and diminished in the sarcoma extracts. The amount of free fatty acids was increased in the melanosarcoma extracts in contrast with the carcinoma extracts.

WILHELM C. HUEPER.

MITOGENETIC RADIATION OF LEUKOCYTES. JACOB KLENIZKY, Biochem. Ztschr. **252**:126, 1932.

Leukocytes emit mitogenetic rays. The spectral analysis of the rays shows bands which are characteristic for glycolysis, oxidation and phosphatase action. There are also bands which are probably due to proteolysis. The quality to emit rays is mainly an intracellular factor. Cell-free exudates show only traces of a glycolytic radiation.

WILHELM C. HUEPER.

STAPHYLOCOCCIC STONES OF THE KIDNEYS. K. BOSHAMER, München. med. Wchnschr. **79**:1951, 1932.

Staphylococcic stones are found primarily in nephritis from various causes, and they are regarded as formed by the precipitation of the proteins of exudates, diluted by the urine, with the bacteria present. This precipitate forms the kernel of the stone around which further deposits of protein, bacteria and inorganic salts collect.

D. O. ROSBASH.

EFFECT OF X-RAYS ON BONE MARROW. ANNIBALE CASATI, Strahlentherapie **43**:582, 1932.

After intensive irradiation of the bone marrow, two phases occur, a degenerative and a regenerative one. During the degenerative phase, the parenchyma cells of the marrow are transformed into connective tissue cells. During the reparatory phase, these cells become again parenchyma cells.

WILHELM C. HUEPER.

EFFECT OF X-RAYS ON CALCIUM AND POTASSIUM METABOLISM. K. ADLER and OTTO WIEDERHOLD, Strahlentherapie **44**:383, 1932.

After large doses of x-rays, a decrease in the potassium and calcium content of the blood serum of rabbits was found. The calcium level decreased by 34.49 per cent and the potassium content by 25.2 per cent. Parallel changes were observed in the calcium and potassium content of the skin after irradiation.

WILHELM C. HUEPER.

ANATOMY OF TUBERCULOUS INFECTION IN MONGOLS. W. STEFKO, Virchows Arch. f. path. Anat. **283**:99, 1932.

Stefko presents a study of tuberculosis as seen in 131 Mongols. From the context it appears that the Mongols were Siberians resident in Russia at the time of death. On gross anatomic grounds Stefko divides tuberculosis, as encountered in his material, into four types: (1) disseminated primary disease of the lung with early involvement of the vessels and secondary involvement of the serous cavities; (2) rapid progress of the process from the primary focus; (3) exacerbation of the primary focus with caseous pneumonia and generalization; (4) primary tuberculosis of the intestine with secondary generalization. He gives the gross and microscopic findings in a characteristic example of each type. Infection began as a bronchiolitis and peribronchiolitis, which spread rapidly and destroyed the local blood vessels. It was then disseminated throughout the lung. Hemorrhage was an early frequent manifestation. The characteristics of the

initial stages are ascribed to structural peculiarities of the bronchial system, which Stefko promises to describe in another communication. He also postulates peculiarities in the structure of the pulmonary vessels that render the latter more susceptible to the destructive action of the infection. In every instance, the tuberculosis was of the infantile or adolescent type. There is a general discussion of the relationship of race and tuberculosis and of the effect of racial constitution and immunity on the course of the infection.

O. T. SCHULTZ.

Microbiology and Parasitology

THE INFLUENCE OF INORGANIC SALTS ON THE MULTIPLICATION OF GONOCOCCUS. C. P. MILLER, JR., A. B. HASTINGS and R. CASTLES, J. Bact. **24**:439, 1932.

Sodium and potassium were found to be interchangeable and nontoxic at high concentration. Calcium and magnesium were unessential but inhibited growth at concentrations greater than 30 millimols per liter. Citrate and oxalate nullified the toxic action of calcium but not that of magnesium. Growth occurred between p_H 6 and 8.2, with optimum growth at from p_H 7 to 7.6. Unless the medium was well buffered either with bicarbonate or with phosphate, growth did not occur. Chloride was replaceable by nitrate or sulphate without impairing growth. Below salt concentrations of 150 and above 550 millimols per liter, growth was inhibited.

FROM AUTHORS' SUMMARY.

HISTOLOGIC CHANGES IN THE BRAIN IN SPOTTED FEVER OF GUINEA-PIGS. MAKATO KODAMA and KENSABURO TAKAHASHI, Zentralbl. f. Bakt. (Abt. 1) **121**:32, 1931.

The authors studied the brains of eighty-six guinea-pigs infected intracardially or intraperitoneally with the virus of spotted fever and examined within two weeks after the termination of the febrile period. In every brain small nodules of glia cells were found, especially (80 per cent) in the gray matter of the cerebral cortex. The authors conclude, therefore, that the four diagnostic points of value in spotted fever of guinea-pigs are: fever, loss of weight, monocytosis and nodules in the brain.

PAUL R. CANNON.

MONOCYTOSIS IN SPOTTED FEVER OF GUINEA-PIGS. MICHIO KONO, Zentralbl. f. Bakt. (Abt. 1) **121**:37, 1931.

Differential blood smears were made from fifteen guinea-pigs infected with spotted fever and from nine healthy controls. During the febrile period there were leukocytosis and lymphopenia. The outstanding feature during the febrile period, in all instances, was the presence of large monocytes, reaching from two to five times the normal number.

PAUL R. CANNON.

YELLOW FEVER IN WHITE MICE. J. E. DINGER, Zentralbl. f. Bakt. (Abt. 1) **121**:194, 1931.

The author has confirmed and extended the observations of Theiler concerning the effects of the yellow fever virus in mice. The intracerebral injection of the virus into white mice caused fatal yellow fever in 100 per cent of the cases, the mice usually dying in from six to eight days with acute encephalitis, with hemorrhages in the stomach, fatty changes in the liver and swelling of the suprarenals and lymph nodes. No specific nuclear inclusions could be found in the ganglion cells.

The virus in the mouse was neurotropic and could not be found during the course of the infection in the blood, spleen, liver or kidneys. It was found, however, in the suprarenals. When emulsions of brain from infected mice were injected into rhesus monkeys, the virus could be recovered from the blood of the latter. Mice could be infected by subcutaneous, intraperitoneal and intramuscular injections

of the virus, but the fatality rate was less and the survival time longer than in the intracerebrally inoculated animals. Survivors were immune to reinjections of the virus.

The virus from the brains of mice was filtrable, and when fed to mosquitoes (Aedes aegypti) was transmitted to monkeys twenty-six days later, both by bites of the mosquitoes and by injection of an emulsion of the infected mosquitoes.

PAUL R. CANNON.

BACTERIOLOGY OF THE SPUTUM OF ASTHMATIC PERSONS. W. STORM VAN LEEUWEN and A. J. STORM VAN LEEUWEN, Ztschr. f. Immunitätsforsch. u. exper. Therap. **76**:109, 1932.

The bacterial flora was studied in the sputum of two groups of asthmatic persons: (1) those whose asthma was caused by house allergens and (2) those whose asthma was bronchitic. The symptoms of patients in the first group disappear in allergen-free chambers. The patients of the second group do not benefit by the foregoing treatment and show no specific skin sensitiveness to any known allergens. No characteristic qualitative or quantitative differences were noted in the bacteria in smears and in cultures. Comparison of the bacteriologic results with skin sensitiveness to bacterial vaccines brought only negative results. The authors conclude that there is no evidence of direct relation between the bacteria of the sputum and the allergic condition. It could not be excluded that the bacterial invasion prepares the ground for allergic sensitization or that it lowers the threshold for the allergens, and so is instrumental in bringing about the asthmatic attack.

I. DAVIDSOHN.

ORIGIN OF BACTERIOPHAGE IN ANIMALS. F. HODER and M. HREBELIANOVICH, Ztschr. f. Immunitätsforsch. u. exper. Therap. **76**:141, 1933.

The bacteriophage found in the stools of guinea-pigs after they had been fed bacterial cultures did not originate within the animal body but was introduced with the cultures. It could always be found in a large amount in the culture before its introduction into the animal. It was directed, as a rule, against heterologous bacteria and was found in the excretion of the guinea-pigs only following the feeding of lysinogenic bacterial species. The great variations in the content of bacteriophage in the cultures was due to a great extent to changes in the sensitiveness of bacteria to the bacteriophage.

I. DAVIDSOHN.

TUBERCULOUS BACILLURIA. S. BADER, Ztschr. f. Tuberk. **65**:202, 1932.

The urine of a hundred patients with severe pulmonary tuberculosis was examined for the presence of tubercle bacilli. Only in five cases in which urogenital tuberculosis complicated the pulmonary disease were tubercle bacilli found.

VIRULENCE OF TUBERCLE BACILLI FROM THE BLOOD IN ACUTE POLYARTHRITIS. GIAN CARLO TORRI, Ztschr. f. Tuberk. **66**:129, 1932.

The recovery of acid-fast bacilli from the blood stream is difficult to interpret if identification is based on smears of sediments and cultural methods alone, as typical apathogenic acid-fast bacilli have been isolated even from normal persons. The author therefore investigated the pathogenicity of ten strains of acid-fast rods isolated by Löwestein's method from nine cases of acute polyarthritis and one of exudative pleurisy. Two-tenths cubic centimeter of a triturated 2 cc. saline suspension of a loopful of each of these cultures was injected subcutaneously into guinea-pigs and intravenously into rabbits and chickens. Nine strains proved to be pathogenic for guinea-pigs, seven for rabbits and two for chickens. Three strains were incontestably human tubercle bacilli. The patients these were isolated

from were all reactors to tuberculin, and two had a pulmonary pathologic process. Five strains were probably avian tubercle bacilli. The relationship of tubercle bacillemia to acute polyarthritis is still unelucidated.

AARON EDWIN MARGULIS.

NORMAL DEVELOPMENT OF TRANSMIGRATION CULTURES OF BACILLUS COLI. GUNNAR FISCHER, Acta path. et microbiol. Scandinav. supp. 9, 1932.

Fischer introduces the term "transmigration culture" (*Transmigrationskultur*) to designate the growth of motile bacteria in semisolid agar. The phenomena manifested by bacteria growing in such medium were first described by Wassén and by Dimitrijevic independently. Fischer reports in great detail his observations on the growth of B. coli. Long test tubes containing 0.2 per cent agar with 2 per cent peptone were used. Single cell cultures of typical and thoroughly studied strains were employed. The characteristic phenomena of the transmigration cultures were due to the motility of the micro-organisms.

After the test tubes of culture mediums were inoculated, a certain time elapsed during which a growth developed on the surface, and then changes took place in the depth of the medium which occurred with striking regularity and which could be assigned to three groups: the-formation of a veil, of one ring and of two rings. All of these formations grew down into the medium and moved through its entire length till they reached the bottom and then disappeared. Behind the rings a zone of clear agar developed.

These growth phenomena developed and moved through the medium according to a definite schedule. As a rule, each strain formed only one type of transmigration growth, but under certain experimental conditions some strains were able to produce all three types. Similar phenomena were observed when the medium was placed in Petri dishes. Here the veil and the rings moved from the inoculated center toward the periphery. However, test tubes proved more satisfactory for the purposes of study. A microscopic study revealed that the rings and the veil were due to accumulations of bacteria, and that the clear zone behind the rings was due to greatly diminished numbers of bacteria. The lower ring, which was the wider of the two, consisted of bacilli measuring from 2 to 7 microns; it displayed an active and characteristic motility, which differed both in speed and in form from the motility of the shorter and narrower bacilli, the accumulation of which formed the upper ring. Above the upper ring the bacilli gradually became shorter and narrower, and lost their motility. In the cultures in which only one ring was seen, microscopic examination showed the presence of an accumulation of the shorter variety of bacilli. The accumulation was not sufficiently dense to be seen with the naked eye. Also, in cultures with veil formation, the microscope revealed a roughly similar distribution of the morphologically different bacilli in the various levels.

All these forms were also found in broth cultures of B. coli, but here they were found in different levels of the test tubes. The bacilli of the lower ring were actively multiplying and were in the logarithmic phase of growth; those of the upper ring were in the phase of negative acceleration, and the bacilli found above both rings were in the maximum stationary phase. The bacilli did not move in any definite direction; their downward motion was the result of a bacteriolytic process taking place at the posterior border of the rings. The anterior border of the ring was perfectly smooth. That was due to differences in surface tension. A certain minimum of nutritive substances was necessary for the development of the cultures. The amount of nutrition determined the speed of the downgrowth. The hydrogen ion concentration, which permitted the development of the culture, ranged from 5.3 to 9.5, with an optimum p_H of 7. The highest concentration of agar which still permitted a downgrowth was 0.5 per cent. The lower the concentration, the faster was the downgrowth. The agar which was passed by the bacteria in their downward growth permitted only a scanty growth of new implants. The inhibition was due to a thermostabile and filtrable toxic substance which was neither

strain-specific nor species-specific. It appeared during the third hour after the inoculation of the medium and was the reason for the termination of the logarithmic phase of the bacterial growth. The used culture medium regained some of its ability to promote growth of bacteria by dilution with distilled water or with plain agar. The effect of the latter depended on the dilution of the toxic substance.

Fischer believes that the toxic substance may be related to, or identical with, the antivirus of Besredka. The bacteriolysis observed behind the rings was due to the lytic agent, which dissolved the motile young bacilli, but did not damage the older, nonmotile forms. The lytic agent has qualities like those of the toxic substance; it differs from the bacteriophage and is not due to microbic dissociation.

In the last chapter some bacteria are listed according to their ability in forming transmigration cultures.

I. DAVIDSOHN.

ACUTE TUBERCULOUS SEPSIS. F. SALTZMAN, Finska läk.-sällsk. handl. **74**:588, 1932.

Reports of seven cases of acute tuberculous sepsis were found in the literature. A new case, fatal after a short course, is reported. Numerous necroses with many bacilli but without tubercles and giant cells were present in the lymph glands, the spleen, the liver and other internal organs. The place of entrance of the infection was not found. There were no old tuberculous foci in the body.

Immunology

SEROLOGICAL STUDIES ON IODINATED SERUM. J. JACOBS, J. Immunol. **23**:361 and 375, 1932.

When iodine is added to animal serums without the presence of acid or alkali, substances are formed which precipitate with antiserums prepared from iodinated serums. This change takes place in the presence of aqueous solutions as dilute as thirty-second normal. Wormall's observation that *di*-iodotyrosine, but not potassium iodide, inhibits precipitation specifically in systems of iodinated proteins and their antiserums was confirmed. The specificity of substances formed in serums iodinated in neutral solutions was tested in several ways. Their specificity is similar to that of other iodinated proteins.

Further evidence of guinea-pig sensitization to compound solution of iodine and guinea-pig serum preparations is described. A much stronger specific sensitization is produced by compound solution of iodine and horse serum preparations. Animals sensitized by these methods are more or less equally susceptible to shock by iodinated guinea-pig and iodinated foreign serums. Evidence is presented which indicates that *di*-iodotyrosine, but not ionic iodine, inhibits shock in these anaphylactic systems.

AUTHOR'S SUMMARIES.

ANTIGENIC SUBSTANCES IN S AND R TUBERCLE BACILLI. C. E. RICE and G. B. REED, J. Immunol. **23**:385, 1932.

The S stype of various strains of acid-fast bacteria, Mycobacterium leprae and human, bovine and avian tubercle bacilli has been found to contain antigenic substances not present in the R type of the same strains, dissociation apparently being accompanied by a considerable loss in antigenic complexity. Immune serums prepared against such S organisms contain certain antibodies reacting with extracts of the homologous S organisms but not with the homologous R type, other antibodies reacting with both S and R types of the same species and a third type of antibody detected by antigens prepared from the other species of acid-fast bacteria, that is, a group antibody. Antiserums prepared against R organisms, on the other hand, appear to lack the S-specific antibody which is found in S antiserum, but contain a much higher proportion of antibodies reacting with extracts prepared from other acid-fast species. The possible chemical nature of the various antigenic substances has been briefly discussed.

AUTHORS' SUMMARY.

ACTIVE IMMUNIZATION OF WHITE MICE BY A NON-POLYSACCHARIDE AND PROBABLY NON-PROTEIN DERIVATIVE OF THE PNEUMOCOCCUS. L. D. FELTON, J. Immunol. **23**:405, 1932.

White mice may be immunized with a fraction of pneumococcus which is soluble in copper acetate in the presence of saturated sodium chloride, and may be extracted with alcohol from the dried copper-free filtrate. This antigen gives a negative Molisch reaction and is probably free from protein. Also no precipitation occurs with antipneumococcus horse serum. The soluble carbohydrates of Avery and Heidelberger in proper dosage prevent the immunizing effect of this antigen. The immunizing antigen has been extracted by the copper method from samples of both type I and type II polysaccharides. Demonstrable immunity is developed in seventy-two hours after intraperitoneal injection and in a shorter time following intravenous injection. Immunity after a single injection of antigen remains maximal for at least three weeks. The immunity conferred on white mice from a single injection is type specific.

AUTHOR'S SUMMARY.

A QUANTITATIVE STUDY OF THE PRECIPITIN REACTION WITH SPECIAL REFERENCE TO CRYSTALLINE EGG ALBUMIN AND ITS ANTIBODY. J. T. CULBERTSON, J. Immunol. **23**:439, 1932.

A method has been described to find the amount of precipitable antibody in a unit volume of rabbit anticrystalline egg albumin serum by the determination of the amount of antigen necessary to neutralize the precipitin of a small volume of the antiserum. At the neutralization point, antigen and antibody combine in a constant ratio to give the maximum precipitate obtainable from the antiserum. Neither precipitinogen nor precipitin remains in the supernatant fluid over the precipitate at the neutralization point. The results obtained by this method are identical with the results obtained by the micro-analytic method for estimating the precipitin content of an antiserum to crystalline egg albumin. The method has proved useful for the accurate determination of the precipitable antibody contained in such an antiserum, especially when only a limited amount of antiserum is available. The quantitative method proposed has been compared with the antigen dilution method and with the antiserum dilution method by the titration of thirty-four antiserums to crystalline egg albumin by the three methods. The results offered indicate that the antigen dilution method, widely used in the titration of precipitating antiserums, is not a satisfactory method to evaluate anticrystalline egg albumin serums according to the amount of antibody contained. Fair correlation is noted between the results of the antiserum dilution method and the results of the quantitative "neutralization" method described here. The neutralization method results in a more exact titer than that arrived at by the antiserum dilution method, since the quantitative method establishes the absolute amount by weight in milligrams of the precipitable antibody contained per cubic centimeter of antiserum. The quantitative method which we have described for the titration of antiserums to crystalline egg albumin is not satisfactory for the titration of antiserums to horse serum.

AUTHOR'S SUMMARY.

A SPECIFIC REACTION OF CONVALESCENT SERUM ON STREPTOCOCCUS FROM POLIOMYELITIS. E. C. ROSENOW, J. Immunol. **23**:455, 1932.

By studying the effect of convalescent serum on streptococci with characteristic cataphoretic velocity, isolated in cases of poliomyelitis, a marked and specific slowing or charge-reducing effect has been discovered. This action of the serum increases during recovery from poliomyelitis, and is at its maximum during the fourth week after the onset of the acute attack, following which it gradually diminishes, but remains readily demonstrable even twenty years after recovery. The reaction is specific, in that the serum of persons and monkeys that have recovered from typical attacks affects the strains both from human beings and from monkeys, in that streptococci and bacteria from other sources than polio-

myelitis are not affected, and in that the reacting antibodies can be removed by absorption only with the streptococcus from poliomyelitis. The results indicate that the streptococcus consistently isolated in poliomyelitis is not a contamination or an agonal or postmortem invader.

AUTHOR'S SUMMARY.

THE HYPOTHETICAL INCORPORATION OF INJECTED ANTIGEN IN RESULTING ANTIBODY. S. B. HOOKER and W. C. BOYD, J. Immunol. **23**:465, 1932.

From the quantitative interrelations of an immune serum prepared by the injection of an arsenic-containing diazo-protein, and as test antigen, a heterologous arsenic-containing diazo-protein, we calculate conservatively that the buchnerian hypothesis, which claims antibody to be a conjugate of injected antigen and body globulin, demands the presence of at least 2.5 and more probably 2,500 times as much arsenic in the immune serum as could possibly be there according to the testimony of direct quantitative chemical tests. The number of chemically defined groups (haptens) entering the molecule during the preparation of a synthetic diazo-protein is determined and shown to agree with the theoretical number. The proportion of protein-combined haptens necessary for visible specific precipitation is approximated for one antigen-antibody system. A suggestion is given as to the number of specific combining groups (antihaptens) in one molecule of the antibody in question.

AUTHORS' SUMMARY.

THE RETICULO-ENDOTHELIAL SYSTEM AND THE SOURCE OF OPSONIN. A. R. ELVIDGE, J. Immunol. **24**:31, 1933.

It is concluded that opsonin production is a function of cells of the reticulo-endothelial system, and that opsonin is a definite chemical substance.

AUTHOR'S SUMMARY.

THE ALLERGIC VERSUS THE TOXIN-ANTITOXIN HYPOTHESIS OF SCARLET FEVER. S. B. HOOKER, J. Immunol. **24**:65, 1933.

The objections to the toxin-antitoxin hypothesis and the arguments in favor of the substituted allergic interpretation are not considered well founded. In addition, it should be borne in mind that although resistance may be sometimes independent of allergy, there is a mass of evidence showing that allergic (specific) inflammation delays bacterial invasion and hastens healing. The allergic cutaneous response is a local expression of the generally enhanced capacity for an unusually rapid development of specific resistance. It is, in general, much more an index of immunity than of susceptibility; the Dick reaction is surely not an index of immunity and so improbably is of an allergic nature. Further, a brief incubation period is characteristic of typical scarlet fever as well as of diphtheria, bacillary dysentery and other diseases the pathogenesis of which rests mainly on the toxigenic property of their incitants. Finally, although there are examples of what may be termed "immunologic" diseases, such as hay fever, the specific antibody concerned somehow in the production of symptoms is not capable of neutralizing the active substance of the extraneous incitant. The neutralizing property of scarlatinal antitoxin is unquestioned. The allergic hypothesis embodies the unattractive and unnecessary conception that both the symptoms and the cure of the disease are mediated by the same neutralizing antibody.

AUTHOR'S SUMMARY.

LOCAL CUTANEOUS SENSITIZATION BY THE PROTEIN OF TUBERCULIN. F. B. SEIBERT, J. Infect. Dis. **51**:383, 1932.

Specific cutaneous sensitization can be produced in normal rabbits and guinea-pigs by repeated injections of the highly purified, undenatured protein of tuberculin. This sensitization is of as high degree, and is of the same type, as that

produced by infection with live tubercle bacilli or by injection of dead bacilli. The most successful methods for preparing and purifying the protein of tuberculin in such a way as to preserve its antigenic capacity were precipitation by means of ammonium sulphate or trichloracetic acid and mere concentration and washing by means of ultrafiltration.

AUTHOR'S SUMMARY.

PRECIPITIN REACTION: EFFECT OF ELECTROLYTES. C. M. DOWNS and S. GOTTLIEB, J. Infect. Dis. **51**:460, 1932.

Certain salts in molar solution inhibit the formation of a precipitate from horse serum and rabbit antihorse serum, but others do not. All the salts studied inhibit the formation of a precipitate from crystalline egg albumin and its antiserum when present in molar solution. The addition of salts does not induce the formation of a precipitate in concentrations of antigen and antibody that fail to give precipitates in the absence of these salts. The washed specific precipitates are soluble in dilute solutions of weak or strong acids and alkalis, and these solubilities are independent of the salt present at the formation of the precipitates. A precipitate when once formed in a dilute solution of a given salt is not soluble in a molar solution of the same salt even though this molar solution can serve originally to inhibit the formation of the precipitate.

AUTHORS' SUMMARY.

ANTIGENIC PROPERTIES OF THE VIRUS OF RABIES. L. C. HAVENS and C. R. MAYFIELD, J. Infect. Dis. **51**:511, 1932.

Rabies virus possesses the property of absorbing the specific antibodies from immune rabies serum. Agglutinin-absorption experiments with nine strains and their homologous serums indicate that differences in antigenic composition exist between strains of this virus. The antigenic dissimilarity shown by agglutinin absorption was confirmed by neutralization experiments. There appears to be at least one component which is possessed by all of these nine strains. The differences observed seem to be due to the presence or absence, in whole or in part, of additional antigenic factors.

AUTHORS' SUMMARY.

LATENT PERIOD IN PASSIVE ANAPHYLAXIS. J. H. LEWIS, J. Infect. Dis. **51**:519, 1932.

The experiments of Friedberger, indicating that the latent period in passive anaphylaxis could be dispensed with by using a homologous sensitizing antiserum, could not be confirmed. With the use of a guinea-pig antituberculoprotein serum of high titer, guinea-pigs can be passively sensitized to a fatal anaphylactic death in not less than four hours after the injection of the sensitizing serum, the same period required for sensitization with a heterologous antiserum. The smooth muscle of the guinea-pig uterus will show anaphylactic sensitization two hours after an intravenous injection of homologous sensitizing serum. An isolated guinea-pig uterus is passively sensitized after remaining in a solution of guinea-pig antituberculoprotein serum for two hours. The uterus is not sensitized after four hours in a solution of rabbit antihorse serum.

AUTHOR'S SUMMARY.

SKIN REACTIVITY TO BACTERIAL FILTRATES. G. SHWARTZMAN, J. Infect. Dis. **51**: 552, 1932.

There exist considerable differences in the neutralizability of meningococcus toxins obtained from various strains of the same serologic groups. The passage of strains of the meningococcus through mediums containing human blood lowers the neutralizability of their toxins by antistock serums. It is suggested that

attempts be made to obtain for therapeutic purposes serums that will neutralize satisfactorily the toxins of strains that have been passed through mediums containing human blood.

AUTHOR'S SUMMARY.

ANTIVIRUS ACTION OF POLIOMYELITIS SERUM. B. F. HOWITT, J. Infect. Dis. **51**: 565, 1932.

Of the serums from twenty-two treated patients who had recovered from poliomyelitis, six (27.2 per cent) gave positive in vitro neutralization of poliomyelitis virus, two (9 per cent) gave partial protection in the monkey and fourteen (63.6 per cent) conferred no protection. Of the serums from twenty untreated patients, eight (40 per cent) showed positive neutralization, one (5 per cent) gave partial protection and eleven (55 per cent) failed to neutralize the virus. Antivirus substances may be present in a certain percentage of treated persons, but apparently those receiving serum treatment show less tendency to produce neutralizing substances than the untreated ones. The patients showing complete recovery after transient or only slight paralysis give more evidence of the production of a potent serum than those in whom severe paralysis develops. The results of these experiments may aid in explaining certain discrepancies in the reports on human convalescent serum therapy in poliomyelitis, and certainly show the need for giving serum from known tested donors, either recovered or naturally immune to the disease. The use of a standardized serum from immunized large animals is indicated.

AUTHOR'S SUMMARY.

PASSIVE IMMUNITY TO CYSTICERCUS FASCIOLARIS IN THE ALBINO RAT. H. M. MILLER, JR., and M. L. GARDINER, J. Prev. Med. **6**:479, 1932.

Passive immunity to infection by a metazoan parasite has been demonstrated. Rats have been protected against infection with Cysticercus fasciolaris, the larval stage of Taenia taeniaformis, by intraperitoneal injections of serum from infected rats or from those actively immunized against this worm. In these experiments serum from infected rats was more effective than that obtained from actively immunized individuals. Serum from rabbits given similar injections of worm material had but slight protective properties. A preliminary attempt to remove the active principle from immune serum was not successful. One cubic centimeter of immune serum per four hundred grams of rat body weight, the highest dilution used, was effective in inhibiting the development of cysts in three of four rats. Complete immunity persisted for twenty-six days, and in two of four rats for thirty-six days, after the injection of immune serum.

AUTHORS' SUMMARY.

THE PHAGOCYTIC FUNCTION OF LEUCOCYTES IN ANAEMIA. F. A. KNOTT and S. J. HARTFALL, J. Path. & Bact. **35**:889, 1932.

The functional activity of leukocytes (phagocytic power) has been estimated in cases of anemia of the anhematopoietic group. In pernicious anemia there is a marked lowering of this function in the stages of severe relapse, with improvement during recovery, but the phagocytic index rarely rises to the normal level. Estimation of the phagocytic power in cases complicated by sepsis has a prognostic value. There is marked depression in aplastic anemia. In simple achlorhydric anemia, even when the degree of anemia is severe, the leukocyte function is much less severely disturbed.

AUTHORS' SUMMARY.

SOME PROPERTIES OF DIPHTHERIA ANTITOXIN IN THE SERA OF ANIMALS OF DIFFERENT SPECIES. M. BARR, J. Path. & Bact. **35**:913, 1932.

Great variations were encountered between the salting-out limits, under the same conditions, of diphtheria antitoxin from serums obtained from actively immunized animals of different species. A considerable proportion of antitoxin

was found to be associated with the euglobulin (water-insoluble) fraction of most serums, particularly goose, rat and cow serums, all of which contained more than one quarter of the total antitoxin in the insoluble fraction. The highest proportion of antitoxin detected in this fraction of horse serum was 2.67 per cent of the total amount; the proportion was increased by the addition before dialysis of normal euglobulin free from antitoxin. The distribution of antitoxin between the two globulin fractions of horse serum bore no relation to the in vivo/in vitro ratio. The antitoxin contained in goose and rat serums was of extremely poor avidity, but a number of other serums showed normal avidity as judged by the value of the dilution ratio. Although guinea-pig and rat serums gave typical toxin-antitoxin flocculations, no satisfactory flocculation was obtained with serums from animals of other species.

AUTHOR'S SUMMARY.

THE PRODUCTION OF IMMUNITY TO VACCINIA VIRUS. R. W. FAIRBROTHER, J. Path. & Bact. **36**:55, 1933.

A high degree of immunity may follow the intracerebral inoculation of mixtures of immune serum and virus inactive on intradermal inoculation. Immune blood has a more marked action on the virus than immune serum. The probable importance of phagocytosis is discussed.

AUTHOR'S SUMMARY.

OBSERVATIONS ON SALMONELLA AGGLUTINATION AND RELATED PHENOMENA. P. B. WHITE, J. Path. & Bact. **36**:65, 1933.

A description of the serologic behavior of p variants of Salmonella typhosus, S. enteritidis and S. aertrycke is given: These three variants are identical in somatic agglutinating and agglutinin-binding properties. The p form does not react with, or fix the agglutinins of, anti-R serums. The R form may or may not agglutinate considerably with anti-p serums; in any case these serums show little or no loss of homologous titer when treated with intact R bacilli. The special serologic properties of the p form, like those of the R form, depend on the presence of carbohydrate haptens. While R bacilli contain a certain amount of the p hapten, apparently in their deeper substance, p bacilli are to all intents devoid of the characteristic R hapten. This relation, indicated by precipitation tests, is supported by the results of agglutinin-fixation tests. It is concluded that the p form is essentially a loss variant of the R form. The properties of a protein (T) extracted from Salmonella bacilli by acid 75 per cent alcohol are also described: Under adequate conditions of extraction the antigen isolated is common to the Salmonella group. Its antibodies, which are quite distinct from those of ordinary S, R or p antiserums, agglutinate alcohol-washed or autolysed R and p bacilli, but fail to clump alcohol-washed S bacilli or young living cultures. This agglutinative difference of the suspensions corresponds with their ability or inability to bind the agglutinins of anti-T serums. The T protein exhausts its antiserum of agglutinins for R and p bacilli. It seems that the T protein, unlike the Q protein previously described, is situated beneath the reactive surface of the living organism and is only exposed by erosion. It is believed that alcohol acidified with hydrochloric acid and variously diluted will prove a valuable reagent in the fractionation of bacterial proteins.

AUTHOR'S SUMMARY.

SPECIES IMMUNITY TO PNEUMOCOCCUS. H. B. DAY, J. Path. & Bact. **36**:77, 1933.

The serologic and immunologic type specificity of pneumococci is due to the presence of type-specific antigens. These are formed by virulent pneumococci during the active phase of their life. With the maturation of pneumococci in aging cultures, preceding obvious or microscopic signs of autolysis, there is formed in their bodies (and later liberated in the surrounding medium) a species antigen. Injection of this antigen in animals induces an active immunity to pneumococci generally; the serum of animals so treated confers a similar passive

immunity on injection. The species antigen appears to be a product of the type-specific antigen which is dissociated through the action of the pneumococcic enzymes into a free antigenic group and type-specific material (nonantigenic). The freed antigenic group in common to all virulent (S) pneumococci, and forms the species antigen. This hypothesis is supported by the following observations: The appearance of the species antigen coincides with the disappearance of the type-specific antigen. The injection of "degraded" (R) pneumococci which contain no type-specific antigen produces no sort of immunity. The reactions of the type-specific and the species antigen to such agents as heat acid and alkali are similar. There is direct quantitative correspondence between the amounts of type-specific and of species antigen needed to induce immunity to any given type of pneumococcus. It is possible to convert type-specific antigen into species antigen in vitro, through the action of pneumococcic enzymes.

AUTHOR'S SUMMARY.

AN ALLERGIC SKIN REACTION AFTER SCARLET FEVER. H. J. GIBSON and J. P. MCGIBBON, Lancet **2**:729, 1932.

In a series of cases of scarlet fever weekly intracutaneous tests were carried out with an extract prepared from cultures of hemolytic streptococci representing the soluble intracellular products of the organisms freed from diffusible substances. A 1:100 dilution of the extract was used. Twenty-eight patients were examined, and in twenty-two the reaction, which was negative during the first week, became strongly positive by the fourth week. The allergic reaction developed in all patients over 7 years of age.

AUTHORS' SUMMARY.

LYSOZYME. A. FLEMING, Proc. Roy. Soc. Med. (Sect. Path.) **26**:1, 1932.

The main points are: That lysozyme is a widely distributed antibacterial ferment which is probably inherent in all animal cells, and constitutes a primary method of destroying bacteria. That lysozyme, while acting most strikingly on nonpathogenic bacteria, can attack pathogenic organisms when allowed to act in the full strength in which it occurs in some parts of the body. That it is easy to make bacteria relatively resistant to lysozyme, so that any pathogenic microbe isolated from the body, where it has been growing in the presence of a non-lethal concentration of lysozyme, must have acquired increased resistance to the ferment. That there are some differences in the lysozyme of different tissues and in different animals whereby bacteria are susceptible to different lysozymes in varying degrees.

AUTHOR'S SUMMARY.

COLD AGGLUTINATION. I. T. MISAWA and T. OHTA, Ztschr. f. Immunitätsforsch. u. exper. Therap. **76**:378, 1932.

The serum of a patient who suffered from syphilis and bronchial asthma, and who belonged to blood group AB, agglutinated at 0 C. the red cells of all four groups. By cooling the serum, a fine sediment was obtained, which agglutinated the red cells of the same person but not of other persons. It did not fix complement in the Wassermann reaction. The sediment was soluble in physiologic solution of sodium chloride at 37 C. The supernatant serum obtained after formation of the sediment agglutinated heterologous red cells and gave a positive Wassermann reaction. Heating for thirty minutes at 63 C. destroyed the cold agglutinins of the sediment. Sediments with similar qualities were obtained from normal bloods possessing cold agglutinins, when the blood was permitted to clot and the serum was separated at 37 C. An immune serum was produced in rabbits by injecting fresh cow's milk. Such serum contains cold agglutinins. A sediment was also obtained from such serum, using the procedure described. Its iso-agglutinins clumped red cells only at low temperatures.

I. DAVIDSOHN.

AUTOHEMOLYSINS IN PAROXYSMAL HEMOGLOBINURIA. T. MISAWA, T. OHTA and K. HEINO, Ztschr. f. Immunitätsforsch. u. exper. Therap. **76**:386, 1932.

Alcoholic extracts of human red cells of all four groups bind the autohemolysin at low temperatures, while alcoholic extracts of the bloods of the horse, ox and goat do not. Under the same condition human red cell extracts also remove the complement from the fresh serum of a patient with hemoglobinuria. At 37 C. the complement remains intact. Alcoholic extracts of the red cells of the ox, horse and sheep do not affect the complement, but extracts of hog red cells act similarly to those of human cells, owing to antigenic qualities which human and hog blood possess.

I. DAVIDSOHN.

RAPID PRECIPITATION REACTIONS WITH HETEROPHILIC ANTISERUMS. JOSEPH MUELLER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **76**:423, 1932.

Rapid precipitation occurred in mixtures of alcoholic extracts of heterophilic tissues and of specific antiserums when proper dilutions of the extracts and proper concentrations of sodium chloride are employed. This was still further improved by the use of concentrated tissue extracts. Cholesterol did not improve the reactivity of the antigenic extracts. When nonconcentrated extracts were employed and the dilutions prepared with physiologic solution of sodium chloride, a precipitation with nonheterophilic serums was observed occasionally, while heterophilic serums did not react. That is due to greater instability of serum globulin in dilutions with low sodium chloride concentrations, while higher concentrations produce a greater stability. The heterophilic precipitate is finer and develops slower than the one observed in reactions between alcoholic tissue extracts and general lipoid antiserums. On the other hand, heterophilic antiserums react more markedly in complement fixation tests, possibly because complement fixation is an expression of a slow and invisible precipitation.

I. DAVIDSOHN.

EFFECT OF HYDROCHLORIC ACID AND OF SODIUM HYDROXIDE ON THE DIFFERENT MANIFESTATIONS OF THE ANTIBODY FUNCTION. GUISEPPE D'ALESSANDRO, Ztschr. f. Immunitätsforsch. u. exper. Therap. **76**:446, 1932.

When lipoid antiserums, produced by injections of lecithin and of alcoholic extracts of horse kidneys, were mixed with proper concentrations of hydrochloric acid and of sodium hydroxide, the complement-fixing and hemolytic properties were destroyed, while the precipitating and agglutinating titers were increased. The required concentration of the acid or alkali is inversely proportionate to the temperature at which the reaction takes place. Other heterophilic antiserums were influenced similarly to the two mentioned previously. Heterophilic immune serums, which commonly lack the ability to agglutinate the red cells of the guinea-pig, acquire this ability after treatment with hydrochloric acid. The addition of dextrose protects the hemolytic properties of the antiserum against the destructive effects of sodium hydroxide but not of hydrochloric acid.

I. DAVIDSOHN.

FORSSMAN ANTIGEN OF PNEUMOCOCCI. M. EISLER and A. HOWARD, Ztschr. f. Immunitätsforsch. u. exper. Therap. **76**:461, 1932.

The report of Bailey and Shorb concerning the finding of the Forssman antigen in pneumococci was confirmed. In the immune serums produced in rabbits with injections of the type I pneumococci there was no antibody against human red cells similar to the one which was produced by injections of Bacillus dysenteriae Shiga and of paratyphoid bacilli. The sheep hemolysin of the immune serum reacted with all types of pneumococci; it was therefore species-specific and not group-specific. B. dysenteriae Shiga and B. paratyphosus did not absorb the sheep lysin produced by the injection of pneumococci, and vice versa. The sheep lysin

was absorbed by the carbohydrate fraction of the pneumococci but not by their alcoholic extract. There was no relation between the amount of Forssman antigen present in the pneumococci and their virulence. An increase of the Forssman antigen was observed following growth on serum and ascites agar, but only in strains which were poor in antigen before, while a decrease was noted following growth in broth of strains with a high antigenic content. In broth to which saponin or sodium taurocholate were added, growth was very abundant, but the Forssman antigen of the bacteria invariably disappeared.

I. DAVIDSOHN.

SENSITIZATION TO PRODUCTS OF ONE'S OWN BODY. W. STORM VAN LEEUWEN and J. VAN NIEKERK, Ztschr. f. Immunitätsforsch. u. exper. Therap. **76**:479, 1932.

Oriel isolated from the urine of allergic patients a proteose, to which the skin of allergic persons reacted, while normal controls did not respond. Van Leeuwen and van Niekerk confirm these findings. In three cases a positive cutaneous reaction was obtained in the patients from whose urine the substance was isolated. It was recently suggested by Murphy and Lobe that the cutaneous reactions against human epithelium reported by van Leeuwen were due to histamine present in human skin. By experiments on a decerebrate cat, and by skin tests in allergic patients with histamine and with properly prepared extracts, the rôle of histamine was excluded.

I. DAVIDSOHN.

ORIGIN OF ANTIBODIES AGAINST LIPOID ANTIGENS AND THE NATURE OF THEIR SPECIFICITY. S. BERGEL, Ztschr. f. Immunitätsforsch. u. exper. Therap. **76**:484, 1932.

The lymphocytes are the origin of antibodies against lipoids. They produce a lipase-like, fat-splitting ferment. Bergel observed the development of agglutinins and of lysins against sheep red blood cells injected into the peritoneal cavities of mice. The product of the lymphocytes acts, at first, nonspecifically, but after repeated treatment with the same antigen, the lymphocytes produce a specific antibody. The peritoneal exudate of animals which were treated repeatedly with tubercle bacilli or with Spirochaeta pallida destroys the homologous antigen, but acts only feebly or not at all on other lipoids. In syphilis, antibodies are developed against the specific spirochetal lipoids and also against the general tissue lipoids.

I. DAVIDSOHN.

Tumors

MULTIPLE PRIMARY MALIGNANT TUMORS. S. WARREN and O. GATES, Am. J. Cancer **16**:1358, 1932.

The cases of multiple malignant tumors collected from the literature number 794. These, the 189 cases of Major, the 143 of Owen, the 93 of Ward and 40 of our own make a total of 1,259. In addition, 37 cases have been cited which we have been unable to verify. On the basis of all statistics, the frequency of multiple malignant tumors in cases of cancer is 1.84 per cent. On the basis of American statistics, the frequency is 3.9 per cent. In our own series of 1,078 autopsies on patients with cancer, the frequency is 3.7 per cent. The average duration from the onset of the earlier tumor to death in our cases is three years. Multiple cancers occur at approximately the same age as single ones. Multiple malignant tumors occur more frequently than can be explained on the basis of chance. Their occurrence may be explained by a predisposition or susceptibility to cancer in certain persons, or by the action of some factor favoring the development of malignancy. The nature of this predisposition is as yet unknown.

AUTHORS' SUMMARY.

ADENOLYMPHOMA (ONKOCYTOMA) OF THE PAROTID GLAND. R. H. JAFFÉ, Am. J. Cancer **16**:1415, 1932.

This paper deals with one of the rare adenolymphomatous tumors which occur in the region of the salivary glands. The epithelial lining of the glands is morphologically identical with a type of cell which develops physiologically in the salivary glands with progressing age and for which Hamperl has suggested the name "onkocytes." In the tumors the onkocytes display marked secretory activity, with the formation of intercellular secretion capillaries. This secretion leads to the formation of small cysts. The lymphatic tissue is not an essential part of the tumor, but is apparently the remnant of a lymph node.

AUTHOR'S SUMMARY.

THE TAR IN CIGARETTE SMOKE AND ITS POSSIBLE EFFECTS. WILLIAM D. MCNALLY, Am. J. Cancer **16**:1502, 1932.

The tar of cigaret smoke contains nicotine, phenolic bodies, pyridine bases and ammonia, irritants which could account for "cigaret cough," the chronic bronchitis of the cigaret smoker, the leukoplakia in heavy smokers and the recorded increase of cancer of the lung. The temperature is not an important factor unless the cigaret is burned to the last centimeter, when the hot smoke becomes more irritating. With a tarry residue of from 4.84 to 15.29 per cent, a definite risk attaches to the smoking of a cigaret, especially since from 6.56 to 11.58 per cent may be absorbed or retained in the body. Cigarets should not be smoked too short, as the last 2 cm. retains most of the tar and other products of incomplete combustion.

AUTHOR'S SUMMARY.

THE ALLEGED CARCINOGENIC ACTION OF TOBACCO TAR. E. BOGAN and R. N. LOOMIS, Am. J. Cancer **16**:1515, 1932.

The results recorded indicate that "whatever carcinogenic properties may inhere in the use of tobacco, they cannot well be ascribed to the chemical effect of the tar derived from distillation of the tobacco."

SPINDLE-CELLED TUMOUR IN A FOWL FOLLOWING INJECTION OF 1:2:5:6-DIBENZANTHRACENE IN A FATTY MEDIUM. H. BURROWS, Am. J. Cancer **17**:1, 1933.

Bilateral spindle cell tumors appeared in one of two white Wyandotte hens at the sites of intramuscular and subcutaneous injections of 1·2·5·6-dibenzanthracene dissolved in lard. An autograft taken from one of these tumors became established and grew. There were metastases in the lung, liver and ovary. Attempts to transmit the tumor to six young chicks by grafting were not successful. A fowl given an injection only of lard as a control died very early in the course of the experiment.

AUTHOR'S SUMMARY.

CORRELATION OF X-RAY PICTURE WITH HISTOLOGY IN CERTAIN BREAST LESIONS. S. P. REIMANN and P. S. SEABOLD, Am. J. Cancer **17**:34, 1933.

Roentgenograms of female breasts were taken at intervals before, during and after menstruation and pregnancy. Fluctuations in the size of the breast tissue proper were found corresponding to these physiologic states. Two typical lesions of the breast were also studied in relation to the menstrual cycle, and were found to fluctuate in size with the stages of the process. These were periductal fibromas (adenofibroma, fibro-adenoma, etc.) and abnormal involution (chronic cystic mastitis, etc.). The lesions were removed surgically, and the histologic features were found to correspond to the theoretical condition for the time of removal in relation to menstruation. Attention to the menstrual phases and their different pictures is necessary for proper pathologic diagnosis of lesions of the breast. Incidentally, many of the names used for various pictures will then automatically

disappear. Ten patients with breasts "painful" just before the onset of the menstrual flow were treated with ovarian residue as recommended by Cutler. In six cases amelioration of the symptoms was obtained. Most patients with this symptom have "shotty" breasts. This can be recorded in the x-ray film, and in three cases thus far investigated in which the symptoms were relieved the "shottiness" was much reduced both to palpation and on films. It is not recommended that removal of doubtful lesions or of malignant tumors be delayed in order to take a series of x-ray films. X-ray films have advantages over transillumination as assistants in diagnosis. Fortunately, large, heavy breasts, which offer the greatest difficulties to palpation, give the clearest x-ray pictures. Also pathologic axillary and pectoral lymph nodes throw shadows, the significance of which will be discussed in another place.

AUTHORS' SUMMARY.

STUDIES ON THE HYDROGEN-ION CONCENTRATION OF THE BLOOD IN CANCER. J. O. ELY, Am. J. Cancer **17**:58, 1933.

In cases of uncomplicated and untreated skin and superficial cancers the blood usually has a normal p_H. In uncomplicated cases of untreated and advanced internal cancers the blood usually has a p_H above normal. The blood of patients with benign tumors usually has a p_H above normal. In a number of pathologic conditions other than cancer the p_H of the blood is elevated as in cancer. In cases of cancer a p_H of the blood which is persistently high in spite of treatment appears to be a bad prognostic sign. The p_H of the blood by itself is of little, if any, diagnostic value in cancer.

AUTHOR'S SUMMARY.

INCIDENCE AND NATURE OF TUMORS IN CAPTIVE WILD MAMMALS AND BIRDS. H. L. RATCLIFFE, Am. J. Cancer **17**:116, 1933.

The incidence of neoplasms in the orders and families of birds and mammals dying in the Philadelphia Zoological Gardens has shown little variation over a period of eleven years. In most orders and families the percentage of animals affected by tumor growth is proportional to the average period of exhibition of the group. That is, as age increases, the incidence of tumors increases. Certain families of both birds and mammals have, however, a much lower incidence than would be expected from the average age for the group. Other avian and mammalian groups have much higher percentages of tumor bearers than the average age seems to warrant. Mammals, generally, are more subject to new growths of the digestive organs and birds to new growths of the genito-urinary organs than to neoplasms affecting other parts of the bodies. The class Aves is, as a whole, less subject to tumor growth than Mammalia.

AUTHOR'S SUMMARY.

SYMPATHETIC TUMORS OF THE ADRENAL MEDULLA. E. SCOTT, M. G. OLIVER and M. H. OLIVER, Am. J. Cancer **17**:396, 1933.

One hundred and fifty-eight cases of tumors with origin in one or both suprarenal medullas have been collected from the literature and classified on the basis of their structural differentiation. Four cases of sympathicoblastomas are reported from the authors' laboratories. A scheme for classification is adopted for sympathetic nerve tumors based on the present conceptions of the histogenesis of the cell types. The Pepper type of tumor of the suprarenal medulla may originate in the right, in the left or in both suprarenals; it frequently occurs congenitally; in the cases reviewed it occurred at an average age of 1.5 months when primary in both suprarenals, of 2.25 months when primary in the right and of 15.5 months when primary in the left; it was found in thirty cases from the literature and in one of the authors' cases; it is found only in the completely undifferentiated class of tumors. The Hutchison type of suprarenal tumor was found in thirty-eight cases from the literature; it may originate in either suprarenal, but was not found when the tumor was primary in both; it occurs at an

average age of 8.5 years when primary in the left suprarenal and at 3.5 years when primary in the right suprarenal. Both Pepper and Hutchinson types originating in the right suprarenal occur at earlier ages than do those arising in the left suprarenal. The younger the patient, the more undifferentiated are the tumor elements. The more undifferentiated the tumor, the greater are the number of metastases and the greater the degree of malignancy. Tumors with atypical metastases occur, as a rule, at older age levels and are more mature in structure. Sex does not appear to be a factor in the incidence of these tumors. The conclusions of Frew as to the relationship of the type of metastasis to the seat of the primary tumor do not seem to be borne out by a study of a larger number of cases. Any attempt at explanation of the underlying factors determining the type of metastasis is at present theoretical. Whether sympathicoblastomas, especially of the Pepper type, are truly metastatic, or whether the foci are heterotopic in origin has been discussed in the literature. According to Wiesel, rests of sympathetic building cells may occur on the undersurface of the liver in early fetal life. It is conceivable that as the liver grows, these cells may be carried into the hepatic tissue with the anastomosis of the vitelline veins and widely distributed with the blood vessels. Matzdorff, also, thinks that the tumors of the liver are not true metastases, but are primary from fetal rests. The distinctly earlier age at which the Pepper type appears might argue for the theory of a systemic origin of this type. However, in the records of all types of malignant sympathetic suprarenal tumors and in case 1 of our series, a probable congenital Pepper type, tumor cells were found filling the lymphatics and blood vessels of both the primary and the secondary growths. This fact is evidence for metastasis as one means of the distribution of the tumors.

AUTHORS' SUMMARY.

CULTURAL CHARACTERISTICS OF CYSTICERCUS CYSTS AND TWO CYSTICERCUS TUMORS. W. MENDELSOHN, Am. J. Cancer **17**:442, 1933.

The growth characteristics of the cells of IRS 146 and IRS 1548 were found to be essentially the same. The growth of IRS 146 and IRS 1548 was composed of malignant cells, connective tissue cells and mononuclear blood cells and macrophages. The characteristic malignant cell has a large, coarsely granular nucleus and a granular cytoplasm. It was found only in cultures of the tumor tissues. The cells which grew in cultures of fetal rat liver were the endothelial and mesothelial cells, the mononuclear blood cells and macrophages and a few hepatic epithelium cells. The growth of the wall of the 4 to 6 month old cyst in cultures consisted of the connective tissue cells, mesothelial cells, mononuclear blood cells and macrophages. The cells which migrated from the explants of the 15 day old vesicle were the endothelial and mesothelial cells, the mononuclear blood cells and macrophages and certain altered cells; these cells were derived for the most part from the rudimentary cyst wall. The supporting elements of the fifteen day infested liver manifest greater growth activity in cultures than those of the non-infested liver of a rat of the same age.

AUTHOR'S SUMMARY.

NEUROFIBROMATOSIS OF THE BLADDER. I. H. KASS, Am. J. Dis. Child. **44**: 1040, 1932.

A boy, 7 years of age, who had had a brown macular eruption of the skin and several subcutaneous nodules since birth, had hematuria of two days' duration. After injection of an opaque medium, roentgen study showed an asymmetric deformity of the bladder; an indurated growth was felt involving and lying between the rectum and the bladder. Death resulted from scarlet fever, bilateral otitis media and bronchopneumonia. The bladder was large, and its wall varied from 2 to 4 cm. in thickness. Numerous tumors projected from the surfaces and extended into the adjacent perivesicular tissue. The tumors of the bladder and the subcutaneous nodules were neurofibromas.

RALPH FULLER.

NEUROBLASTOMA OF THE ADRENAL WITH MULTIPLE METASTASES. JACOB KLEIN, Am. J. M. Sc. **184**:491, 1932.

A case of neuroblastoma (medulloblastoma) of the right suprarenal gland in a girl, aged 2½ years, is reported. The right suprarenal gland was completely replaced by an encapsulated tumor, which was soft in consistence and on section had a dark red, granular appearance. Microscopically, the tumor cells were arranged in groups (pseudorosettes), some of which showed necrosis in their centers. Glia fibers were demonstrated in the tumor by Hortega's method and by Mallory's glial stain. There was extensive visceral involvement (Pepper type) combined with numerous metastases in the lymph nodes, calvarium, humerus, ribs, orbital fat, liver, lungs and spleen.

SANDER COHEN.

IMMEDIATE CAUSES OF DEATH IN CANCER. SHIELDS WARREN, Am. J. M. Sc. **184**:610, 1932.

The immediate cause of death has been studied in 500 cases of carcinoma. Cachexia is the most frequent single cause, although exceeded by the total of the various pulmonary disorders. Cachexia is associated most frequently with cancer of the breast, stomach and large bowel. By far the commonest cause of death in carcinoma of the cervix uteri is renal insufficiency. Sepsis is an unimportant factor in fatal cases. The striking association of carcinoma of the buccal mucosa with pneumonia (36.2 per cent) and with abscess of the lung (56.3 per cent) emphasizes the rôle of aspiration in the production of these lesions.

AUTHOR'S SUMMARY.

MULTIPLE BENIGN CYSTIC EPITHELIOMA. F. SUMMERILL and J. G. HUTTON, Arch. Dermat. & Syph. **26**:854, 1932.

This comparatively infrequent tumor begins as a rule about the time of puberty or earlier, usually in female patients. It is symmetrical in distribution and usually appears on the face, but may occur on the neck, the chest, the upper parts of the arms and rarely on the lower limbs. It may affect two generations in succession, but rarely occurs in the third. It develops from the basal cells of the epidermis or hair follicles. It does not appear to change into basal cell carcinoma.

ACUTE LEUKEMIA FOLLOWING LYMPHOSARCOMA. KATSUJI KATO and ALEXANDER BRUNSCHWIG, Arch. Int. Med. **51**:77, 1933.

Two cases are reported in which the patients when first seen had lymphosarcoma with a normal blood picture; a short time later acute lymphatic leukemia developed, with a rapidly fatal termination. This is additional evidence in favor of the view that lymphosarcoma and lymphatic leukemia are different stages in the same pathologic process. Roentgen therapy was instituted in both cases immediately after the diagnosis of lymphosarcoma was made, and the question therefore arises as to whether or not this treatment induced the leukemic state.

AUTHORS' SUMMARY.

SQUAMOUS CELL CARCINOMA OF THE KIDNEY. J. RABINOVITCH, Arch. Surg. **24**:581, 1932.

A case of squamous cell carcinoma of the kidney is reported in which the tumor invaded the renal artery and produced complete infarction of the kidney.

N. ENZER.

ADAMANTINOMA. R. F. C. KEGEL, Arch. Surg. **25**:498, 1932.

Kegel reviews thirty-five cases. There seems to be a higher incidence of this tumor in the colored race. The majority of the tumors are located in the lower

jaw. The earliest age of incidence was 7 years; the oldest, 73; the majority of the cases occurred in persons of the ages between 11 and 35. The growth is slow and the duration long, and the tumor may reach a considerable size. Necrosis and fistulas occur. When the tumor involves the upper jaw, it usually extends into the antrum. Roentgen examination shows a central bone expansive tumor. The tumor may be polycystic or solid. The fundamental cell type is a basal epithelial cell with varying degrees of differentiation into enamel. The stroma may or may not be cellular. Keratinization, with epithelial pearls, alveolar formations and frequently papillary formations, is found. Mucoid degeneration of the stroma is common.

N. ENZER.

ADAMANTINOMA: REVIEW OF REPORTED CASES. JOSEPH MCFARLAND and H. M. PATTERSON, Dental Cosmos **73**:656, 1931.

Adamantinomas arise in the jaws from the paradental epithelial débris and in the hypophysis from the squamous epithelial débris of the hypophyseal duct. Irritation may be a causative factor in these tumors in the jaws, but probably not in the pituitary gland. Adamantinomas, in whatever location, have approximately the same histologic structure. They are locally malignant but generally benign. They do not metastasize. (The two cases reported by Simmons seem to be exceptions.) They cannot be definitely diagnosed until exploratory operation and biopsy are performed. They usually occur in the upper and lower jaws and in the pituitary gland, but cases occurring elsewhere have been reported, two in the tibia, one in the upper lip and a doubtful one in the nasomalarpalpebral region. Adamantinomas of the jaws are more common than those of the pituitary gland. One hundred and sixty-six cases in the jaw have been reported. These occurred in women and men in the proportion of three to two; the average age of the patients at the time of entering the hospital was 40 years; the average duration of symptoms was seven years. They occurred in the lower and upper jaws in the proportion of five to one, and twice as often in the left side of the lower jaw as in the right side. In the upper jaw the two sides were evenly affected. There were about six cystic to one solid tumor. Only complete radical excision seems able to effect a cure. Twenty-six cases of adamantinoma of the pituitary gland have been reported, 90 per cent of which were suprasellar. The average age of the patients was 24 years, and the average duration of symptoms, three years. The two sexes were about equally affected. About 95 per cent of these tumors were cystic. Operation is always indicated but seldom curative, satisfactory results having been obtained in only three cases.

We were able to collect references to one hundred and ninety-six cases of adamantinoma in the medical and dental literature.

AUTHORS' SUMMARY.

STUDY OF THE CAUSATIVE AGENT OF A CHICKEN TUMOR. J. B. MURPHY and E. STURM, J. Exper. Med. **56**:705, 1932.

The inhibiting factor present in certain relatively slow-growing strains of chicken tumor I and in chicken tumor X is adsorbed from extracts of the desiccated tumors by aluminum hydroxide (Willstätter type C) and can be released in effective quantities from this combination by treatment with basic sodium phosphate.

AUTHORS' SUMMARY.

EFFECT OF TESTICLE EXTRACT ON THE GROWTH OF CHICKEN TUMOR. I. E. STURM and F. DURAN-REYNALS, J. Exper. Med. **56**:711, 1932.

Extracts prepared from the testicular tissue of the rat, rabbit, fowl or bull, when injected together with extracts of chicken tumor I or with cells of this tumor, showed no definite effect of either enhancement or inhibition so far as concerned the resulting tumors.

AUTHORS' SUMMARY.

TUMOR-LIKE CONDITIONS IN RABBITS CAUSED BY FILTRABLE VIRUS. R. E. SHOPE, J. Exper. Med. **56**:793 and 803, 1932.

A tumor-like condition has been observed in a wild cottontail rabbit and has been found to be transmissible to both wild and domestic rabbits but not to guinea-pigs, white rats, white mice or chickens. The clinical picture of the experimentally produced condition and the pathologic picture of the original and of the experimentally produced tumors have been described. The tumor has the general appearance of a fibroma. The methods used in transmitting the condition and satisfactory routes of inoculation have been described and discussed.

The properties of the agent causing a tumor-like condition in rabbits have been tested experimentally and the conclusion reached that it is a filtrable virus. While the tumor-like condition and infectious myxoma differ markedly in their clinical and pathologic pictures, they have been found to be related immunologically. The relationships of the tumor-producing virus to the virus of infectious myxoma and of the tumor-like condition to malignant neoplasms have been discussed.

AUTHOR'S SUMMARIES.

SOME PHYSIOLOGICAL CHARACTERISTICS OF EPITHELIAL TUMORS OF THE MOUSE. L. SANTESSON, J. Exper. Med. **56**:893, 1932.

The histologic and physiologic characteristics of mouse tumor in vitro have been compared. Twenty-eight adenomas, thirty-one adenocarcinomas, eighteen carcinomas and a series of tumors from two transplantable carcinomas and from Ehrlich carcinoma were cultivated in vitro. The adenomas were characterized by cells of normal appearance, migrating quickly and organizing in thin membranes, a few mitoses, a large production of acid and a rapid digestion of fibrin and egg albumin. The carcinomas differed from adenomas in a less rapid and less extensive migration of epithelial cells, a tendency to grow in budlike formations, the presence of many mitoses, a lesser production of acid and a lesser digestion of fibrin and albumin. Ehrlich carcinoma differed from both adenomas and spontaneous carcinomas in the unhealthy state of the cells, their irregular growth and the occurrence of a great many mitoses. The production of acid was slight, and the digestion of egg albumin or fibrin less marked, and even entirely lacking.

AUTHOR'S SUMMARY.

CANCER SUSCEPTIBILITY IN RELATION TO COLOUR OF MICE. C. C. TWORT and J. M. TWORT, J. Hyg. **32**:557, 1932.

An examination of about 10,000 tumor-bearing mice appertaining to 240 experiments comprising 24,000 animals has been made to find whether there was any difference in sensitiveness of the skin to our carcinogenic agents according to the color of the coat and eyes. Self-colored animals (excluding pure white) were more sensitive to petroleum oils (weak agents) than the corresponding piebald ones; that is, a black was more sensitive than a black and white, etc. When tars (strong agents) were utilized instead of petroleum oils, an opposite state of affairs existed, the self-colored animal being more resistant than its piebald companion. This reversal may be explained on the grounds of cell tolerance. Pink-eyed animals (excluding pure white) had a greater all over sensitiveness of the skin to our agents than animals with pigmented eyes. On the whole, the most sensitive animal was the pink-eyed fawn. The frequency of hyaline degeneration of the spleen and marked thyroid enlargement was greater among pink-eyed animals, especially when fawn-colored, than among animals with pigmented eyes.

AUTHORS' SUMMARY.

Society Transactions

CHICAGO PATHOLOGICAL SOCIETY

PAUL R. CANNON, *President, in the Chair*

Regular Monthly Meeting, March 13, 1933

HYPERTENSION COINCIDENT WITH RETROPERITONEAL GANGLIONEUROMA AND MULTIPLE AREAS OF SOFTENING IN THE BRAIN AND THE SPINAL CORD OF A YOUNG MAN. FLOYD H. JERGESEN.

Hypertension (the blood pressure varying from 250 systolic and 120 diastolic to 274 systolic and 140 diastolic) was observed in a man 23 years of age. A ganglioneuroma, histologically moderately mature, was found in the retroperitoneal region, near the left kidney. The brain and spinal cord contained multiple foci of hemorrhagic softening. There was marked arteriosclerosis of the vessels of the brain, spinal cord and kidney, with moderate involvement of the arterioles of the heart and mild involvement of those of the lungs, liver suprarenal glands, pancreas, intestines and skeletal muscles. The left testis contained no mature spermatozoa. Although hypertension not otherwise explainable has been observed associated with paragangliomas which are embryologically related to the tumor in this case, it is believed that the high blood pressure in this patient can be explained best on the basis of generalized vascular and renal changes. The presence of the ganglioneuroma probably was only coincident.

HISTOPATHOLOGY OF TONSILS HARBORING STREPTOCOCCUS EPIDEMICUS IN PATIENTS WITH AND WITHOUT ARTHRITIS. I. PILOT.

In septic sore throat due to Streptococcus epidemicus a considerable number of patients become carriers of this organism. The tonsils as a rule remain enlarged and reddened, and exudate is present in the crypts. Some of the carriers have acute rheumatic polyarthritis indistinguishable from acute rheumatic fever. Others complain of persistent pains in the joints without signs of inflammation. Still others do not have arthritis or arthralgia but may have glomerulonephritis, endocarditis, erythema nodosum or related rheumatic manifestations.

Tonsillectomy was performed when the rheumatic symptoms became quiescent excepting in patients with arthralgia or persistent arthritis. These patients had symptoms in the joints which usually were relieved after the removal of the tonsils. The carrier state was terminated by excising the tonsils. Throat cultures for Str. epidemicus rapidly became negative. Cultures of the extirpated tonsils revealed these streptococci in predominant numbers and even in pure culture. Histologic examinations were made. All the tonsils showed chronic inflammation. The crypts often contained exudate cells, epithelium and bacteria. The lining epithelium at times was replaced by granulation tissues. Bacterial stains revealed cocci in crypts on the surface epithelium or deeper in the underlying lymphoid tissue which was infiltrated with polymorphonuclear or plasma cells. The cellular reaction in the tonsils of the patients with arthritis did not differ from that in the tonsils of those without arthritis. It is evident that the tonsil may be a focus of infection due to Str. epidemicus. In addition to the focus and the streptococci, an underlying hypersensitiveness of the articular tissues is

necessary for the development of articular symptoms. The improvement following the removal of the focus, terminating the carrier state for Str. epidemicus, indicated that these streptococci as well as other hemolytic streptococci are important factors in the etiology of rheumatic arthritis and arthralgia.

DISCUSSION

R. H. JAFFÉ: Nodules of granulation tissue are found around the capsule of the tonsil. The portals of entrance may also be the points of excretion of the organism.

MULTIPLE CARCINOID TUMORS OF THE ILEUM WITH REGIONAL METASTASES: REPORT OF TWO CASES. ELEANOR M. HUMPHREYS.

In two cases, occurring in white men, 60 and 66 years old, multiple carcinoid tumors were found in the ileum. In the first there were nine nodules from 6 mm. to 2 cm. in diameter, and in the second, two nodules measuring 5 mm. and 1.4 cm. The nodules had the gross and microscopic appearance of carcinoid tumors. Silver-reducing granules were demonstrated in the tumors in the first case, but staining with silver was not attempted in the second because of the long interval between death and autopsy. In both cases there were metastases in the regional mesenteric lymph nodes. The proof of relationship cannot be considered absolute in the second case because of the coexistence of other malignant tumors (in the lungs and the esophagus). However, the histologic evidence strongly favors the view that the growths in the mesenteric nodes were metastases from the intestinal tumors. In neither case were there any known symptoms referable to the primary or the secondary tumors, although the largest nodule in the first case had produced a definite narrowing of the lumen.

Carcinoid tumors of the small intestine, originally considered benign infiltrating neoplasms, are potentially or frankly malignant if the ability to form metastases is taken as a criterion. Including the two reported, at least thirty cases with regional or distant metastases are on record. Multiple tumors are more common than some of the reports indicate. With these two there are at least forty-one recorded cases, with nodules numbering from two to more than thirty.

In recent reports the relationship of these tumors to symptoms of acute or chronic intestinal obstruction has been emphasized. The manner in which stenosis and resulting symptoms are produced was well illustrated in the first case. Examination of a series of nodules of increasing sizes shows that two factors are concerned. The increase in size of the initial nodule, located chiefly in the submucosa, leads to the formation of a sessile or a slightly pedunculated polyp. The extension of tumor tissue into the outer coats is commonly accompanied by scarring and contraction of the serosa and muscularis. Thus narrowing results from a combination of reduction of the circumference of the intestine with the development of a polyp which still further reduces the lumen.

CARCINOID TUMOR OF THE RECTAL COLON. ALEXANDER BRUNSCHWIG.

A carcinoid tumor of the rectal colon, 5 mm. in diameter, occurred 8 cm. above the mucocutaneous junction of the anus. It was excised under local anesthesia. No symptoms had been referable to the growth. There seems to be no other report of carcinoid tumor in the rectal colon proved histologically by silver impregnation. A carcinoid tumor must be considered in the differential diagnosis of epithelial tumors of the rectal colon.

The complete report was published in *The Journal of the American Medical Association* (**100**:1171 [April 15] 1933).

VERRUCOUS AORTITIS WITH SPECIAL REGARD TO ANEURYSM FORMATION IN CHILDREN. B. H. NEIMAN.

In a series of 4,100 consecutive autopsies at the Cook County Hospital, verrucous aortitis was found 3 times. The first observation was in the body of an

11 year old white girl and the clinical diagnosis was rheumatic heart disease. In addition to the verrucous aortitis, there were rupture of the aorta above the valve, verrucous endocarditis of the mitral and aortic valves, and Aschoff nodules in the myocardium. The second observation was in the body of a 27 year old colored woman, in whom the condition was associated with acute myocarditis. In the third body, that of a 4 year old white girl, the verrucous aortitis was associated with an aneurysm which ruptured into the pericardial sac. The aorta had verrucae; the myocardium, inflammatory scars.

Histologic studies in all demonstrated productive endarteritis. In a circumscribed focus the infecting agent causes a fibrinoid swelling, the first reaction. Should this go on to a productive change, there is a proliferation of fibrocytes, round cells and large histiocytes. Necrosis then breaks the internal elastic membrane, the media and even the adventitia. Should the weakened wall be unable to support the force of the blood pressure, a rupture or an aneurysm results.

In the 11 year old girl, because of the Aschoff nodules in the myocardium, the aortitis was on the basis of rheumatic fever. In the 27 year old woman, acute myocarditis of nonspecific origin was found. In the 4 year old child, streptococci were demonstrated in the lesion and scars in the myocardium. This case was one of streptococcic aortitis with an end-result identical with that of rheumatic aortitis.

The vascular verrucae are similar to, if not identical with the endocardial verrucae. They are manifestations of endarteritis with productive, proliferative changes. Inflammatory changes of the aorta may result not only from the vasa vasorum, but also by way of the lumen. In the latter there is productive endarteritis.

Regular Monthly Meeting, April 10, 1933

FRANK MCJUNKIN, *Vice-President, in the Chair*

REGIONAL PATHOLOGY IN AMERICA. WILLIAM F. PETERSEN.

Presentations were made of maps indicating the geographic distribution of mortality in the United States for the following diseases: exophthalmic goiter, leukemia, pernicious anemia, diabetes, tuberculosis, poliomyelitis, syphilis, tabes, dementia paralytica, erysipelas, gastric ulcer and angina pectoris. The presentation involved a discussion of meteorological and other factors presumably involved in the distinct regional distribution of such diseases. In this the underlying physiologic mechanisms apparently operative are to be sought in periodic anoxemic stimulations.

A FATAL INFECTION BY CLOSTRIDIUM WELCHII IN A PATIENT WITH PULMONARY TUBERCULOSIS. H. C. SWEANY and ASYA STADNICHENKO.

Although Howard reported on nine patients with a terminal Welch bacillus infection arising in the gastro-intestinal tract, no record was found of an infection in a tuberculous patient. Sailer, Laws and Eiman described a patient in whom such a condition arose without preceding disease. The important feature was the development of a profound toxemia with an effect on the suprarenals resulting in a gradual lowering of the blood pressure.

In a similar case the process appeared to begin in the gastro-intestinal tract of a patient with a stationary type of advanced pulmonary tuberculosis. Beginning rather insidiously with hyperpyrexia, abdominal pain, collapse and lowered blood pressure, it ended in death within fourteen days. Necropsy twelve hours after death revealed the old tuberculous process in the right lung, moderate-sized tuberculous ulcers in the intestines and a gangrenous segment of the lower ileum, about 170 cm.

in length. There was no strangulation or thrombosis of the mesenteric artery. The liver extended to the third rib on the right and the third interspace on the left. On surfaces made by cutting, it was soft and slate gray. Other changes were relatively unimportant. There were numerous large gram-positive bacilli in the blood and all the organs. This micro-organism was an encapsulated anaerobe. It produced a "foamy" liver within eighteen hours in a rabbit killed ten minutes after intravenous inoculation. Cultural reactions (milk, agars, sugars, etc.) permitted classification of it as a presumptive type III Cl. welchii.

DISCUSSION

E. F. HIRSCH: Postmortem or agonal invasion of tissues by these bacteria may have occurred.

H. C. SWEANY: The clinical progress coincided with Cl welchii infection.

GENERALIZED LYMPH GLAND REACTION IN A TRANSITIONAL CELL CARCINOMA OF THE NARES. GEORGE MILLES and N. D. FABRICANT.

The response of the lymph glands of the body to stimuli depends on the nature and severity of the stimulus and the time during which it may act, as well as on the susceptibility of the various components of the lymph gland.

The following case illustrates these features:

A white man, 23 years of age, began to suffer from severe pain involving the right side of the head in April, 1931. This was followed shortly by progressive enlargement of the cervical glands, which in December, 1931, responded to radium. The enlargement recurred, however, and was resistant to roentgenotherapy.

He entered the Research Hospital in August, 1932, with severe pain limited to the right side and back of the head and pruritus of the right side of the nose and lips. His breathing was obstructed, his speech was garbled, and he was markedly emaciated. The skin was anemic, and a massive lobulated firm swelling occupied both sides of the neck. The right naris was completely obstructed and the left partially obstructed by large polypoid masses. The palate and pharynx bulged, and the mucous membranes were dry and thick. Enlarged lymph glands were noted in the armpits and groins, and the liver was large.

The blood had a moderate anemia, 1 per cent lymphocytes, 2 per cent large mononuclears and transitionals, 83 per cent neutrophilic polymorphonuclears and 14 per cent eosinophils. The urine contained blood, 4 + albumin and casts. The roentgenogram disclosed increased density over the right maxilla and nasal cavity, with involvement of bone. Lymph glands from the inguinal region showed a marked lymphoid and plasma cell proliferation with numerous eosinophil leukocytes. A cervical gland disclosed marked fibrosis with hyalinization, a dense infiltration with plasma cells and eosinophils and marked proliferation of the reticulum cells with the formation of large cells having one or two nuclei.

During the following month he was septic, and finally the respiratory obstruction became so marked that a tracheotomy was made. He died one week later.

At autopsy the palate was firm and infiltrated. The retropharyngeal mass was an abscess lined with lobulated friable tan tissue and communicating with a similar pocket in the left side of the neck. The glands here were enlarged to 3 cm., and in the center they were broken down. Similar firm enlarged glands were found in the mediastinal, abdominal, axillary and inguinal groups.

Microscopic sections of the nasal tissues revealed islets of anaplastic transitional epithelial cells surrounded by a dense plasma cell and eosinophilic infiltration. Metastases were present in many of the cervical glands. Some of them had the same reticulum cell and plasma cell proliferation found in the biopsy tissue. Similar changes were present in the abdominal and axillary glands.

A dissociable, pleomorphic streptococcus was isolated ante mortem from the blood stream as well as post mortem from the cervical lesions.

From the pathologic standpoint the difficulty of arriving at a definite diagnosis from the biopsy specimen received is apparent. However, the real difficulty came in the interpretation of the marked plasma cell response in association with an atypical or peculiar proliferation of reticulum cells and their apparent derivatives. From a study of the sections, transitions between mature lymphocytes, irritation forms and typical plasma cells can be readily traced. Similarly, transitions between the atypical large mononuclear forms and the occasional multinucleated cells, forms which in some instances are indistinguishable from Hodgkin's disease, from the reticulum cells can be seen.

Similarly the occurrence of a marked reticulum cell response may be associated with the development of a variety of atypical cells including giant cells, generally held specific for Hodgkin's disease.

Therefore, while Hodgkin's disease is an entity and its identification is based not only on its individual cell components — but more especially on their arrangement and numbers with relation to each other — not uncommonly the clinical features must be known to interpret correctly the changes found.

RECURRENT ECTOPIC PREGNANCY COINCIDENT WITH TUBERCULOUS SALPINGITIS. P. A. DELANEY.

A white married woman, aged 34, entered the hospital on Jan. 4, 1933, because of acute lower abdominal pain of twenty-four hours' duration that had become increasingly severe. She also complained of an accompanying sense of pressure against the bladder and rectum. On Dec. 9, 1932, she had experienced an initial attack of acute pain in the right upper quadrant, near the midline, that was controlled with morphine. About a week later she had slight menstrual "spotting" with backache and daily emesis; her last normal menstrual period had been late in November, 1932. Her past history was significant in that about eight years previously she had been operated on for a ruptured ectopic pregnancy of the right fallopian tube. She stated that she had never had any other pregnancy, nor had she ever had symptoms of tuberculosis.

The clinical diagnosis of left tubal pregnancy was confirmed at operation on Jan. 5, 1933, and a left salpingectomy was performed. Grossly the ostium of the oviduct was open, and the enlarged portion of the ampulla contained clotted blood and placental tissue but no embryo. The lower part of the ampulla and the isthmus were within normal dimensions; their mucosa or endosalpinx had prominent longitudinal folds and multiple small gray nodules. The serosa was everywhere smooth and without nodules. Microscopically, sections from the enlarged ampullary portion showed normal placenta while the rest of the ampulla and the isthmus had a hyperplastic glandular mucosa with ciliated bordering epithelium and multiple miliary tubercles. Solitary acid-alcohol-fast bacilli were found in different parts of the lower ampulla and isthmus. Unfortunately no pathologic report of the right tube removed eight years previously is available.

Tuberculous salpingitis complicating ectopic pregnancy is a relatively rare condition. In 1921, Greenberg, reviewing cases from the Johns Hopkins Hospital, reported that in 200 cases of tuberculous salpingitis there had been no associated ectopic pregnancy, and that none of 303 cases of ectopic pregnancy showed any tubal tuberculosis. In 1930, Behney, in his thorough study of 167 consecutive cases of ectopic pregnancy, reported a single case, while Urdan published a clinical study of 474 cases which failed to include any type of pelvic tuberculosis. Van Etten, in 1931 reported 1 case in 77 patients with tubal pregnancies operated on at Sloane Hospital, New York, from 1926 to 1930. A review of the literature for the past decade renders it apparent that the prevalent idea that tuberculous salpingitis is a frequent factor in the etiology of ectopic pregnancy is ill-founded.

AMERICAN SOCIETY FOR EXPERIMENTAL PATHOLOGY

C. PHILLIP MILLER, *Secretary*

Twentieth Annual Meeting, The University of Cincinnati, Cincinnati,

April 10, 11 and 12, 1933

PEYTON ROUS, *President, in the Chair*

A FILTRABLE VIRUS FROM A PANDEMIC DISEASE IN RABBITS. LOUISE PEARCE, PAUL D. ROSAHN (by invitation) and C. K. HU (by invitation), Rockefeller Institute for Medical Research.

In December, 1932, a highly contagious and fatal disease broke out with explosive force in our rabbit-breeding colony; it spread so rapidly that within a month every animal in the colony of 1,500 rabbits had been infected.

Clinically, the disease resembled smallpox in man, and we have given it the name of "rabbit-pox." It was characterized by fever, prostration, general adenopathy and a pocklike eruption of variable extent on the skin and mucous membranes. The incubation period was from five to ten days. In typical cases, the first sign of infection was the appearance of erythematous macules; in these areas papules then developed which later became umbilicated and covered with crusts. The lesions varied in size from minute points to nodules 1 cm. in diameter. They occurred singly, in groups or as confluent masses with extensive edema and, in some cases, with hemorrhage. The eruption occurred over the entire body but was most extensive on the ears, the eyelids and eyebrows, the lips, the nape of the neck, the trunk and the scrotum. The mouth, tongue, nose and pharynx were frequently involved, and a seromucous, purulent or clear blood-stained discharge from the nose was common. Ocular lesions were likewise of frequent occurrence, and in males the testicles usually showed nodular or diffuse orchitis with edema of the scrotum.

The degree and the course of the infection varied widely. In cases of severe infection the majority of the rabbits were markedly prostrated and were evidently extremely ill, but some animals with extensive lesions appeared to be in perfect health. Many animals showed an apparently complete recovery from a severe infection, the visible lesions healing with scar formation. Death frequently occurred within a few hours after the first signs of the infection were noted or after a period of days or weeks. The mortality varied with the breed, sex, age and physiologic status. Among animals under 2 weeks of age, the mortality approximated 100 per cent, but it decreased with age, until in normal adults it was less than 20 per cent. In the animals of Himalayan stock there were no deaths among adults, while in others, such as the Belgian rabbits, the death rate was extremely high. Abortions were frequent.

The acute phase of the pandemic lasted about four weeks. After this time, the daily incidence of fresh cases and of deaths dropped fairly abruptly. In general, the later cases were milder than the earlier ones, this being particularly noticeable in the young animals; however, instances of severe disease did occur.

The postmortem observations were variable and not always characteristic. The organs most consistently affected were the liver, the spleen and the lungs. In typical cases, the liver was enlarged, pale yellow and firm and showed numerous small, opaque, gray or pearly white nodules. The spleen was enlarged, dark red and firm and usually showed focal lesions comparable with those in the liver. The lungs as a rule showed similar small focal lesions and areas of consolidation or lobar pneumonia. Focal or diffuse lesions were found in many organs and tissues, including the suprarenal glands, ovaries, testicles, salivary glands, lymph nodes, bone marrow, subcutaneous tissue, fat, muscles and periosteum.

Histologically, the lesions showed a central area of necrosis surrounded by a zone of edema or hemorrhage and infiltration with mononuclear cells. Inclusion bodies were not found.

Experimental transmission of the disease was attempted early in the course of the pandemic. Since the results of bacteriologic examination and the clinical picture made it appear unlikely that we were dealing with any of the usual bacterial agents, the initial experiments were carried out with Berkefeld V filtrates of various organs and tissues injected intratesticularly. In other experiments, unfiltered suspensions were used. The organs employed included: testicles, liver, spleen, lungs, popliteal lymph nodes, brain, spinal cord, blood and skin. The results of the first experiments were successful in that orchitis and scrotal edema were pronounced within forty-eight hours, fever developed, the animals appeared ill and death occurred in from four to eight days. This condition has been produced successively from rabbit to rabbit by means of filtrates (usually testicular), and the agent is now in the fifteenth serial passage. Other routes of infection have also been successfully employed, namely, intracutaneous, subcutaneous, intravenous, intraperitoneal, intramuscular and intracerebral injection and nasal and conjunctival instillation.

It has been possible to reproduce all the clinical and pathologic features of the spontaneous disease, including recovery, by the use of small doses and certain routes of infection, in particular intravenous injection and nasal and conjunctival instillation.

The limits of dosage are high. Very small amounts are sufficient to produce pronounced lesions, and death has followed the intratesticular injection of 1 cc. of filtrate in a dilution of 1:8,000. Berkefeld N filtrates are also active. Unfiltered material, however, is much more potent than filtered material; 0.2 cc. of a dilution of 1:1,000,000 injected intradermally produces a definite lesion with swelling, edema, hemorrhage and necrosis. The agent is active in tissues stored in 50 per cent glycerin at icebox temperature for at least ninety-four days.

Recovery from either the spontaneous or the experimental disease is associated with a refractory state to reinoculation. Furthermore, the serum from animals that have recovered has the property of neutralizing the virus in a 1:1 serum-virus mixture, as shown by intracutaneous tests.

The identification of the virus is not yet complete. There is apparently no relationship with the agents of virus III disease of rabbits and of infectious myxoma as shown by cross-inoculation and by virucidal tests, and clinically and pathologically the conditions do not resemble each other. (The experiments with infectious myxoma were carried out by Dr. T. M. Rivers.) There is likewise no clinical resemblance to Shope's tumor. We understand from Dr. Carl Ten Broeck, who is making comparative experiments, that rabbits recovered from Shope's tumor and from this tumor plus infectious myxoma show an increased resistance to the rabbit-pox virus.

With respect to vaccine virus, there is apparently some relationship but not complete identity. Rabbits immunized with the New York City Board of Health vaccine virus were refractory to rabbit-pox filtrates variously applied, but intradermal injections of unfiltered pox virus resulted in a positive but highly modified cutaneous reaction. Adult rabbits immunized with vaccine virus do not contract rabbit-pox when exposed to "open" cases, but young immunized rabbits do. In these instances, the disease was considerably milder than that presented by normal control animals (litter mates). Furthermore, serum from animals immunized with vaccine virus has a definite, but only a partial, protective power against rabbit-pox virus. We have not been able to produce lesions typical of vaccinia in either the scarified cornea or the skin, but cytoplasmic inclusion bodies have been found in the corneal epithelium of early experimentally induced lesions. It should be noted that we have worked with only one strain of vaccine virus and have not yet employed the neurotropic strain.

Studies on the host range of the virus are in progress. We have not succeeded in infecting rats, but in one instance the virus was recovered from the testicle of a guinea-pig into which the material was injected intratesticularly. Mice have

been infected by the intracerebral route. With this procedure, death occurs in from four to six days, and the brain contains active virus. The virus is now in the fifth serial mouse-to-mouse passage. Animals of other species, including the calf, will be tested for susceptibility.

There have been reports of epidemics of generalized vaccinia attributed to neurovaccine. It is not certain whether this disease falls in this category, but the present indications are that it is not a generalized vaccinia as the term is ordinarily understood.

It should be mentioned that this was not the first time we had encountered the disease. Early in 1930 there occurred several examples of a comparatively mild infection in a small breeding colony shortly after the importation of some rabbits from Europe. We thought that we had been successful in eradicating the condition, and there were no recognizable cases until this last winter, approximately three years later. Whatever the source of the present pandemic may have been, it is obvious that the disease is a possible menace to a laboratory in which rabbits are employed and that, under certain circumstances, it may be an extremely serious one.

THE PATHOGENESIS OF TRICHINOUS MYOCARDITIS. GLEN L. DUNLAP (by invitation) and CARL V. WELLER, University of Michigan.

Although the histopathologic picture of trichinous myocarditis as seen in fatal human cases is well understood, there has been much uncertainty as to whether the characteristic inflammatory reaction is due to the presence of embryos in the wall of the heart or to toxic substances brought to the heart by the blood stream. Encysted forms are never found in the cardiac muscle. It has been shown experimentally that in white rats to which an adequate number of encysted embryos has been administered young embryos in active migration can be found in the interstitial tissue of the myocardium for a short period only, roughly from the eighth to the eleventh day after feeding. Coincidentally, a defensive inflammatory reaction is established. After the twelfth day, the invading organisms disappear from the myocardium and are never found encysted in fibers of the cardiac muscle.

FAMILIAL FACTORS IN ARTERIOSCLEROSIS IN RABBITS. PEARL M. ZEEK, University of Cincinnati.

The inbreeding of rabbits for about three years has resulted in the establishment of two strains (living under identical conditions); one is apparently free from arteriosclerosis, while in the other this lesion occurs spontaneously with an incidence of about 30 per cent.

THE CHEMICAL CONSTITUTION OF THE PROSTATIC CORPORA AMYLACEA AND PROSTATIC CALCULI. ROBERT A. MOORE and R. F. HANZAL (by invitation), Western Reserve University.

Microchemical and histochemical studies demonstrate that the prostatic corpora amylacea are composed fundamentally of nucleic acid and its hydrolytic products. Some of the nucleic acid is in combination with a protein, probably a protamine, and some is probably in combination with calcium. A small amount of lipoid, probably lecithin and sphingomyelin, is incorporated. It is possible that there is also some independent carbohydrate aside from that incorporated in the nucleic acid. Such a chemical composition is in harmony with the morphology of these structures. The larger calculi are composed essentially of the same constituents, plus an infiltration with crystalline and noncrystalline calcium phosphate and calcium carbonate.

FERTILITY IN THE MALE. DAVID L. BELDING, Evans Memorial of the Massachusetts Memorial Hospitals.

In order to evaluate fertility by examination of spermatozoa in human beings it is necessary to establish normal standards. The total number of spermatozoa per emission and the rate of production, as determined from a series of specimens, form

a good index of testicular activity. Some degree of correlation exists between a persistent low count and a low level of fertility. The viability of spermatozoa depends on the condition of the spermatozoa, the temperature at which they are held and the menstruum. Under favorable conditions spermatozoa have been kept alive for twenty-six days. Before spermatozoal morphology can be used as a basis for determining fertility, it is necessary to differentiate the immature and atypical forms which occur in fertile persons from the abnormal forms indicative of sterility.

AN EFFECT OF ANTERIOR PITUITARY HORMONE (PROLAN B) ON FLEXNER-JOBLING CARCINOMA OF RATS. O. M. GRUHZIT, Research Laboratories, Parke, Davis and Company, Detroit.

Considerable effort has been spent in the last few years in an endeavor to repress neoplastic growths by the use of various tissue extracts. Recent reports indicate the possibility of the inhibition of the growth of transplantable tumors in mice by the administration of potent extracts obtained from the urine of pregnancy. This extract, when given to immature or to nonpregnant female mice, hastens ovulation and luteinization as do the extracts of the anterior lobe of the pituitary gland. The extract is known as prolan B.

In a series of experiments, adult male rats were inoculated with Flexner-Jobling carcinoma and forty-eight hours after the inoculation were placed under treatment with from 250 to 500 rat units of prolan B daily for from twelve to fourteen days. Some of the control animals remained untreated; others were treated with phenolated water or with protein material obtained in the process of preparing the active hormone extracts. In addition, the anterior pituitary growth hormone was used for comparison. One hundred and twenty-four animals received prolan B and 110 control animals either remained untreated or received nonspecific treatment. Tumors developed in 87.5 per cent of the 124 animals treated with the hormone, and there was no effect in 12.5 per cent. Tumors developed in 88.9 per cent of the 62 untreated controls, and there was no effect in 11.1 per cent. Of the 48 animals treated with phenolated water, nonspecific protein and the anterior pituitary growth hormone, there was no effect in 13.8 per cent, and in 86.2 per cent tumors developed. The results suggest that the hormone obtained from the urine of pregnancy, when used in doses of from 250 to 500 rat units a day, caused no higher incidence of repression of tumor growth than occurred in the control group. The rate of growth of the tumors was the least in the animals treated with prolan B, in which it differed only slightly from that in the animals treated with phenolated water. The greatest rate of growth was noted in the control animals and in those treated with the growth hormone. It was similarly evident that the gain in weight was the least in the animals treated with huge doses of prolan B. The decreased rate of growth of the tumors in these animals was probably indirectly due to the same factors which interfered with their systemic well-being.

These experiments suggest that the retardation in the rate of growth of Flexner-Jobling carcinoma in rats was probably due to the nonspecific toxic effect of the extracts. The incidence of tumors in treated animals did not differ from that in untreated controls or in animals treated with nonspecific substances.

THE SEROLOGIC REACTIONS OF A NEW PROTEIN FROM MILK. L. S. PALMER and JULIAN H. LEWIS, University of Minnesota and University of Chicago.

The fat emulsion in cow's milk is stabilized by a layer of adsorbed material firmly held at the surface of the fat. If not the only, at least the most important substance acting as a stabilizer is a protein which can be isolated from cream after repeated dilution and reseparation by centrifugation. Although this process removes all soluble solids, the fat emulsion is as stable as in the original cream. When the emulsion is broken by churning and the butter fat removed by warming to 60 C. and pouring off, an aqueous solution remains which contains a protein that can be precipitated at a p_H of from 3.9 to 4. The general chemical composition of this protein, as well as the physical and chemical properties of its aqueous solution,

shows that is is not casein, lactalbumin or lactglobulin. Immunologic methods were used to differentiate it further from the other proteins of milk. The "membrane" protein acted as a good antigen, since guinea-pigs sensitized with it gave fatal anaphylactic reactions when the protein was injected intravenously. Slight reactions were obtained when animals sensitized with the membrane protein were given injections of casein and lactalbumin, but not when they were given the alcohol-soluble protein of milk. With lactglobulin, fatal reactions were obtained. Animals sensitized with the membrane protein and desensitized to casein, lactalbumin and lactglobulin reacted fatally to the homologous proteins. Identical results were obtained when sensitized uterine strip preparations were used. These experiments indicate that the membrane protein is distinct from the other milk proteins, but that it shows a relationship to them, probably based on species specificity, which is more pronounced with lactglobulin.

THE INFLUENCE OF THE LIVER ON THE DESTRUCTION OF BILE SALT. J. L. BOLLMAN and F. C. MANN, Mayo Clinic.

We have studied the excretion of bile salts in the urine of dogs following ligation of the common bile duct with extirpation of the gallbladder and following removal of the liver. We have modified the method of Gregory for the determination of bile salts so that it is adequate for the determination of fairly large amounts of the salts.

During the first day following ligation of the common bile duct and extirpation of the gallbladder, a very small amount of bile salts is excreted in the urine. The excretion then rises to about 500 mg. daily, and remains fairly constant for some time. The feeding of additional amounts of bile salts (1 or 2 Gm. daily) fails to increase the excretion materially. The intravenous injection of bile salts permits the recovery in the urine of approximately 50 per cent of the added salts. It appears that the dog with biliary obstruction is able to destroy or to fix considerable amounts of bile salts.

Following removal of the liver, the excretion of bile salts is not of sufficient magnitude to give a definite reaction with the Gregory method. Bile salts given intravenously, however, are almost completely recovered in the urine within twelve hours after administration. Destruction of bile salts does not occur in the absence of the liver.

CHEMICAL FINDINGS IN THE BLOOD AND URINE IN PATIENTS WITH SEVERE DAMAGE OF THE LIVER. STEPHEN MADDOCK, Boston City Hospital.

(No abstract furnished.)

EXPERIMENTAL HEPATIC INSUFFICIENCY PRODUCED BY MODIFIED ECK FISTULA AND ROENTGEN IRRADIATION. F. W. HARTMAN and V. SCHELLING, Henry Ford Hospital, Detroit.

The difficulty of producing marked hepatic insufficiency in dogs with high voltage roentgen irradiation alone led to the development of a modified Eck fistula, which may be performed in one stage and has a low mortality. The use of high voltage roentgen irradiation in combination with the Eck fistula produces readily controlled insufficiency with little cirrhosis. The functional studies demonstrate the difficulty of the bilirubin method when less than 3 mg. per kilogram is used, and show that the change in ratio between free cholesterol and cholesterol esters is a valuable diagnostic aid.

ATTEMPTED IMMUNIZATION OF RABBITS AGAINST EXPERIMENTAL SYPHILIS. G. E. WAKERLIN (introduced by A. J. CARLSON), University of Louisville.

In an attempt to produce artificial active immunity against experimental syphilis in rabbits, fourteen animals were each given a total of sixty-five injections, at four day intervals of 1 cc. of an extract (in physiologic solution of sodium chloride) of syphilitic rabbit testes, containing from five to six dead Spirochetae pallidae (Nichols strain) per dark field. In one half of the animals the preparation was

injected into the right testis, and in the other half it was given subcutaneously. Another group of eight rabbits was similarly treated with a control extract prepared from normal rabbit testes, one half of the animals of this group receiving injections intratesticularly and the other half subcutaneously.

The Wassermann reactions of all of the rabbits remained consistently negative during the two hundred and sixty day period.

Subsequent to the completion of the attempted immunization, in both groups of rabbits, as well as in a second control group of four untreated rabbits, the right testis was inoculated with the homologous strain of living S. pallida. Within the limits of individual variation, the incubation period of the active syphilitic infection, the severity and duration of the local lesions, the incidence and severity of the metastatic lesions and the duration of the positive Wassermann reaction were identical for each of the three groups.

The method of attempted immunization employed, therefore, was unsuccessful in the production of local testicular or generalized active immunity to experimental syphilis in the rabbit.

THE OCCURRENCE OF MONONUCLEAR PHAGOCYTES IN THE INFLAMMATORY EXUDATE IN LOBAR PNEUMONIA AND THEIR RELATION TO RESOLUTION. O. H. ROBERTSON, University of Chicago.

Certain striking histologic changes which we observed took place regularly in pneumonic lungs of dogs at the time of recovery from experimental pneumococcic pneumonia led to a study of the consolidated pulmonary tissue of human beings dying at different stages of lobar pneumonia.

We were fortunate to secure the lungs of a patient who died of nephritis six days following recovery from lobar pneumonia. The histologic picture of the lungs of this patient was very different from that observed in patients dying of the disease. The alveolar walls were markedly thickened, the alveoli were largely air-containing, and the cells of the exudate consisted chiefly of large mononuclears. The thickening of the alveolar walls was due to a general swelling of the septal cells, certain of which were partially detached from the walls and appeared to be entering the aveolar spaces.

A number of other cases showing varying stages of resolution were studied, and it was possible to follow this change from its beginning to the height of the reaction.

The earliest evidence of the production of mononuclear cells is the appearance of an occasional swollen lining cell of the septum. They also arise from the endothelium of the capillaries and probably from other structures of the supporting framework. As the reaction proceeds, more and more cells of the alveolar wall hypertrophy, become detached and gradually replace the polymorphonuclear leukocytes in the alveolar exudate.

These cells are actively phagocytic after they enter the alveolar spaces, and they appear to increase in size, many of the free cells being much larger than those in the alveolar walls. They appear to digest pneumococci rapidly, as many poorly stained forms are seen within them, and wherever resolution has progressed there are few or no pneumococci. The macrophages also engulf polymorphonuclear leukocytes and red blood cells.

Another possible function of the macrophages is that of the disposal of fibrin. When seen in the midst of a fibrin mass, they are usually surrounded by a clear zone, suggesting that the fibrin is being dissolved by enzymatic activity. Fragments of fibrin are also seen within the cells.

These observations in human beings, as well as those in dogs, suggest that the local development of large mononuclear phagocytes constitutes one of the important factors in bringing about resolution of the pneumonic exudate. Supporting this conception is the constant finding of this macrophagic reaction wherever resolution is occurring and its absence in consolidated areas which fail to show resolution.

OBSERVATIONS ON REPEATED ATTACKS OF EXPERIMENTAL PNEUMOCOCCIC LOBAR PNEUMONIA IN DOGS. L. T. COGGESHALL (by invitation) and O. H. ROBERTSON, University of Chicago.

Employing the method previously described for the production of experimental pneumococcic lobar pneumonia in the dog (*J. Clin. Investigation* **12**:433 [March] 1933), we made a study of repeated attacks of the experimental disease. The constant relationship observed in our earlier work between the infecting dose and the outcome of the disease made it possible to determine with certainty whether a dog which had recovered from one attack was more or less susceptible to a subsequent infection. These observations include twenty dogs undergoing sixty-four infections produced at intervals of from three days to nine months.

It was found that the dogs which recovered from one attack of the disease survived subsequent infections induced by doses that regularly caused death in the initial attack. Furthermore, the secondary infections were mild and rarely involved more than a single lobe. Other evidences of the increased resistance of these dogs included: (1) the much reduced incidence and degree of bacteremia, (2) the occurrence of leukocytosis after infecting doses that regularly caused leukopenia in the primary attack and (3) the beginning development of the "macrophage reaction" in the pulmonary lesion within a few hours after its inception.

A study of the pneumococcidal activity of the blood serum showed that this property of the blood was irregularly present following the first attack or subsequent ones and had no apparent relationship to the dog's resistance to pneumococcic infection.

Tests were made on fifteen of the animals to determine whether or not hypersensitiveness to the pneumococcus developed as the result either of the primary attack or of the recurrent attacks of pneumonia. For this purpose a salt solution-pneumococcus autolysate was injected both subcutaneously and intrabronchially. No evidence of an allergic reaction was observed.

PROTECTION OF THE PERITONEUM AGAINST INFECTION. BERNHARD STERNBERG and HARRY GOLDBLATT, Toledo Hospital and Western Reserve University.

Heat-killed colon bacilli suspended in tragacanth were introduced into the peritoneal cavity of dogs. The mixture provoked an intense polymorphonuclear response of the peritoneum. Subsequent infections of the peritoneum, lethal in control dogs, were prevented, and the animals survived. The protection against infection and death is present within twelve hours after the introduction of the Bacillus coli-tragacanth mixture. The protection is due to phagocytosis of living bacteria by the polymorphonuclears already present in the peritoneal exudate. The phagocytosis is not specific since the polymorphonuclears evoked by the B. coli-tragacanth mixture ingest bacteria other than B. coli. This intense local polymorphonuclear response is due to the retention of the bacteria within the peritoneal cavity by the tragacanth.

THE EFFECTS OF LOCAL IMMUNIZATION ON THE DEVELOPMENT OF EXPERIMENTAL ABSCESSES OF THE LUNG. W. McC. TUTTLE (by invitation) and PAUL R. CANNON, University of Chicago.

Dogs were immunized against Bacillus coli and Staphylococcus aureus by spraying a vaccine prepared from formaldehyde-killed organisms into the main bronchi with a pressure spray apparatus introduced through a bronchoscope.

At intervals varying from fourteen to twenty-one days an embolus infected with homologous cultures of B. coli and Staph. aureus was introduced into the left external jugular vein. An embolus thus introduced lodges in the lungs and in normal animals gives rise to an abscess.

The animals were killed after varying periods up to thirty days, and the lesions were studied grossly and microscopically. Normal animals and animals immunized subcutaneously were used as controls.

The results indicate that lesions in the locally immunized animals are in general smaller and more sharply circumscribed than those in the controls. In some of the locally immunized dogs the embolus was surrounded by a dense wall of young fibroblasts and macrophages, within ten days, at which time well developed abscesses with irregular borders were present in the controls. Phagocytosis is prominent in the locally immunized animals, and repair is distinctly farther advanced than in the control after similar periods. Local immunization of the lungs, therefore, enhances the ability of the pulmonary tissues to overcome invading micro-organisms and to repair the local damage caused by them.

TISSUE EXTRACT AND BLOOD CLOTTING. H. P. SMITH, E. D. WARNER (by invitation) and K. M. BRINKHOUS (by invitation), State University of Iowa.

An extract of perfused pulmonary tissue in saline solution contains large amounts of thromboplastin or thrombokinase. This substance is instrumental in the conversion of prothrombin into thrombin. Pure pulmonary extract will not coagulate pure fibrinogen, even though calcium is present. We are, therefore, unable to accept the "tissue fibrinogen" theory of clotting as advocated by Mills. The clotting which does occur at times is slow and is due to contamination of the reagents with prothrombin or thrombin. Our experiments show that extremely minute traces of such impurities cause this slow type of clotting.

EXPERIMENTS ON THE CHEMOTROPISM OF LEUKOCYTES. MORTON MCCUTCHEON and WILLIAM B. WARTMAN (by invitation), University of Pennsylvania.

Experiments were made to determine whether polymorphonuclear leukocytes are attracted by dead leukocytes. Human blood was centrifugated, and a small clump of leukocytes (from about 300 to 500 microns in diameter) was placed on a slide and allowed to dry. A drop of fresh blood from the same person was placed on the dead leukocytes and allowed to spread between the slide and the coverslip. The preparation was examined with the microscope at 37 C. The dead leukocytes were placed at one end of the microscopic field, and the number of leukocytes which moved to the dead ones and made contact with them was counted. Another field without dead leukocytes was then studied, and the number of leukocytes that made contact with an area of the same size as the clump of dead leukocytes was counted. In ten experiments, the number of moving leukocytes that made contact with the dead ones was eleven per hour; the number in the control fields making contact with the corresponding area was two per hour. It is therefore concluded that in these experiments polymorphonuclear leukocytes were attracted by dead cells.

SELECTION OF RETICULO-ENDOTHELIAL CELLS WITH THE MAGNET: METHOD AND FINDINGS. PEYTON ROUS and J. W. BEARD (by invitation), Rockefeller Institute for Medical Research.

Numerous functions are attributed to the phagocytic cells situated along the blood stream in certain organs, notably the liver, spleen and bone marrow. We have procured such cells from the liver by dislodging them with a stream of fluid after they have taken up an iron compound and sorting them out from the associated elements with a strong electromagnet. The cells thus procured exhibit characteristic features which they retain on cultivation.

THE FATE OF BLOOD PLATELETS. RAPHAEL ISAACS, Thomas Henry Simpson Memorial Institute for Medical Research, Ann Arbor, Mich.

From serum suspensions, stained by Wright's method, of cells of bone marrow, spleen and lymph nodes taken at biopsy, operation and autopsy, the tinctorial and morphologic changes in phagocytosed blood platelets have been studied. Platelets appear to be taken up in the spleen by large cells of the type that contain hemo-

siderin and other granules. They become less basophilic, and the aggregates of material become more compact and appear as groups of deep reddish-staining granules, with a faint element of blue. The granules finally disintegrate and become indistinguishable from the general structure of the cytoplasm of the phagocytic cells. In a spleen removed at operation from a patient with thrombopenic purpura, active decomposition of platelets in the cytoplasm of the phagocytic cells was noted, although the number in the peripheral blood was practically negligible. These platelets must have been from blood received by a transfusion or platelets produced by the patient himself but destroyed too rapidly.

THE DIFFERENCE IN THE CREATINE CONCENTRATION OF THE LEFT AND RIGHT VENTRICULAR MUSCLES OF THE HEART. DAVID P. SEECOF, CHARLES R. LINEGAR (by invitation) and VICTOR C. MYERS, Western Reserve University.

Embryologic, anatomic, pathologic and physiologic data were assembled which led to the idea that the muscles of the left and right ventricles were qualitatively different. Studies of the creatine concentration established chemical differences between the two ventricles.

The findings in the hearts of eighty-four patients from birth to 83 years of age examined within thirty-six hours post mortem and in nine fresh animal hearts obtained from the abattoir are presented. The concentration of creatine was found to be higher in the left ventricle than in the right. In human beings, the creatine content in the left ventricle ranged from 116 to 369 mg. per hundred cubic centimeters of blood and in the right ventricle, from 93 to 283 mg. In this series, the creatine concentration in the left ventricle averaged 211 mg., and in the right, 148 mg. The average absolute difference between the left and right ventricles was 63 mg., or 30 per cent. The series of animals showed creatine contents averaging 308 mg. per hundred cubic centimeters of blood for the left ventricle and 265 mg. for the right, an average absolute difference of 43 mg., or 14 per cent.

An analysis of the findings indicates that the variations in the creatine content of the left and right ventricles may be correlated with the age, the weight of the heart, the creatine content of the voluntary muscles and the retention of creatinine in renal disease.

The fact that the two ventricles have different creatine contents further supports the idea that separate consideration must be given to the left and right ventricles "in all attempts to unravel the exact mechanism of the ventricular pump."

PATHOLOGICAL SOCIETY OF PHILADELPHIA

Regular Meeting, April 13, 1933

V. H. MOON, *President, in the Chair*

CONGENITAL HEART DISEASE WITH PULMONARY ARTERITIS: INTERVENTRICULAR SEPTAL DEFECT, DEXTROPOSITION OF THE AORTA AND DILATATION OF THE PULMONARY ARTERY. HAROLD L. STEWART and BAXTER L. CRAWFORD.

The following case presented a rare combination of cardiac defects consisting of a solitary opening at the base of the interventricular septum, dextroposition of the aorta and dilatation of the pulmonary artery instead of the stenosis which is usually present in the tetralogy of Fallot. In association with these anomalies, there were well developed inflammatory and degenerative lesions in the pulmonary artery and in its branches. The patient, a previously healthy, noncyanotic white

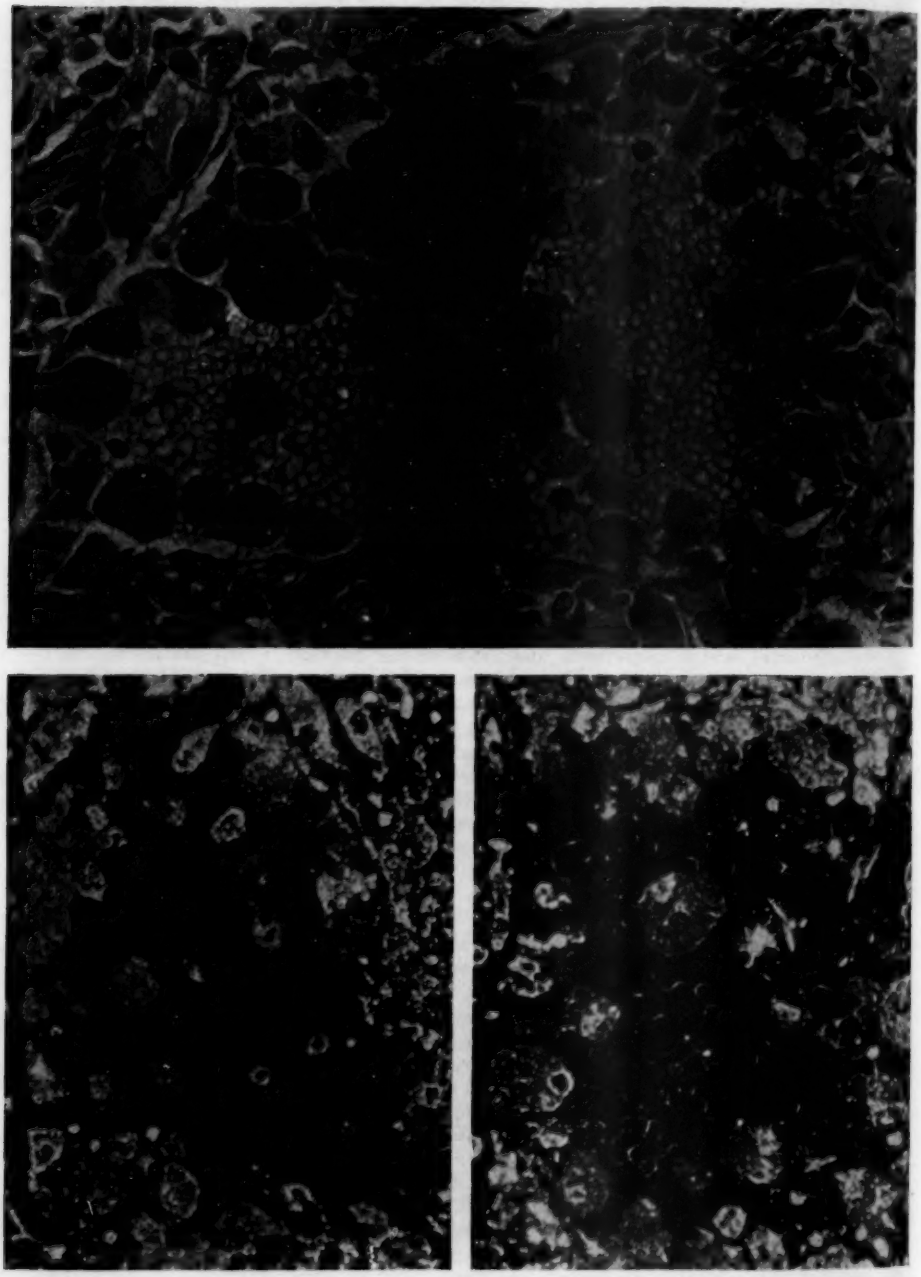
man, aged 60, a painter, gave no history of syphilis or rheumatic fever. Signs and symptoms of congestive heart failure developed, from which he died nine months after the onset.

The heart weighed 600 Gm. All the chambers except the right ventricle were dilated; the walls of both ventricles were markedly hypertrophied; the musculature contained numerous firm, grayish-yellow streaks and flecks. In the upper part of the ventricular septum there was a large funnel-shaped defect which measured 1 by 2.5 cm. and tapered from left to right, opening into the sinus of the right ventricle beneath the septal cusp of the tricuspid valve. The wall of the conus was hypertrophied. The lumen was somewhat narrowed as the result of compensatory hypertrophy of the crista supraventricularis which formed the anterior margin of the defect on the side of the right ventricle, screening the opening of the defect from the interior of the conus which opened into a dilated pulmonary artery. The pulmonary cusps were irregularly widened. The commissures were widened, and the free margins rolled inward. There were several massive aggregations of calcific material on the anterior and the right posterior pulmonary cusps. Above the cusps the pulmonary artery was dilated, inelastic, finely scarred and irregularly thickened by discrete and confluent atheromatous plaques. The aorta, which presented several patches of atheroma and calcification, was shifted to the right, overriding the ventricular septal defect so that it appeared to arise from both ventricles. The foramen ovale was closed, and the ductus arteriosus was obliterated. There were extensive thrombosis of the larger branches of the pulmonary artery and multiple infarction of the lung. Microscopically, the intima of the pulmonary artery and its branches was retracted by underlying scars and was irregularly destroyed and considerably thickened by atheromatous, calcific, fibrous and hyalinized plaques which penetrated deeply, replacing large portions of the media. The internal elastica was split, frayed and reduplicated, and in places it was much reduced. The intima contained a few small plaques consisting of necrotic cells with distorted and elongated nuclei, leukocytes and multinucleated cells. In the adventitia there were nodular and linear collections of lymphocytes, plasma cells and proliferating fibroblasts about the vasa vasorum, which were markedly thickened. The inflammatory tissue projected fanwise into the media, forming stellate scars which interrupted and replaced the muscularis and elastica. The smaller pulmonary arterial branches (3 mm. and less) were thickened, fibrosed and occasionally thrombosed; the internal elastica presented hypertrophy or atrophy, splitting, fraying and reduplication. The vessels were frequently surrounded by perivascular granulation tissue containing in some instances many lymphocytes, plasma cells and newly formed capillaries and at other times large amounts of connective tissue which sent stellate projections into the pulmonary parenchyma.

The patient died at the age of 60, which is almost double the highest age ever before attained by a patient with this combination of cardiac defects. As the anatomic conditions in the heart favored oxygenation, the admixture of venous with arterial blood was negligible, which accounts for the absence of clubbing of the fingers and until the last illness the absence of dyspnea and cyanosis. The relatively high pressure in the left ventricle, the healed pulmonary valvulitis, the contour of the ventricular septal defect and the patches of fibrosis on the endocardium bordering the defect and on the wall of the conus opposite support this assumption. The ventricular septal defect probably contributed to longevity by permitting the force of both ventricles to combine in propelling blood through the lesser circuit against the resistance offered by the sclerosed pulmonary arteries. With the onset of myocardial insufficiency, the shunt through the defect became venous arterial. The main branches of the pulmonary artery presented the characteristic lesions of degenerative atherosclerosis, which is rare with this combination of cardiac defects. In addition there was a well marked inflammatory lesion which had the characteristic appearance of those described as syphilitic, although the changes were not present in the aorta and there were no other lesions suggesting syphilis. The Wassermann reaction unfortunately was not determined. The lesion may possibly have been due to rheumatic fever, although it was not characteristic of that disease.

INCINERATION OF THE SPLEEN IN GAUCHER'S DISEASE. ESMOND R. LONG.

Recent extensive use of incineration in the study of various pathologic as well as normal tissues suggested its application as a supplement to other histologic methods in a case of Gaucher's disease that came under observation. The patient



Incineration of the spleen in Gaucher's disease.

was a 7 year old girl under the care of Dr. H. Epstein, who will report the case in detail later. The spleen was removed at the Jewish Hospital of Philadelphia. The diagnosis before operation was Gaucher's disease, and this was confirmed by microscopic study of sections and by chemical analysis. The latter, made by Dr. J. G. Reinhold at the Philadelphia General Hospital, disclosed the presence of 6.2 per cent kerasin, a finding now considered distinctive for Gaucher's disease, or cerebroside-cell hepatosplenomegaly, in the differential diagnoses of the lipoidoses (Epstein: *Virchows Arch. f. path. Anat.* **281**:152, 1931).

The incineration study was made to determine whether a corresponding accumulation of inorganic material accompanies that of the cerebroside kerasin. The technic used was that of Policard (*Ann. d'anat. méd.-chir.* **1**:163, 1924; *Protoplasma* **7**:464, 1929) and Scott (*Compt. rend. Soc. de biol.* **190**:1073 and 1323, 1930; *Proc. Soc. Exper. Biol & Med.* **29**:349, 1932; *Am. J. Path.* **8**:329, 1932).

In general, the Gaucher cells were found to have a high content of ash in the nucleus and a low content in the cytoplasm as illustrated in the accompanying figure. Most investigators who have reported on incineration of tissues have called attention to the nuclear ash. In the study here reported the same peripheral distribution of ash was noted as described by Scott and Horning (*Am. J. Path.* **8**: 329, 1932) in the nuclei of tumor cells and by Cowdry (*Am. J. Path.* **9**:149, 1933) in the nuclei of liver cells in yellow fever. The nucleoli conspicuous in the sections stained with hematoxylin and eosin could also be observed in the ashed specimens, although not with regularity.

There was nothing distinctive in the distribution of the ash in the cytoplasm. Iron salts, which can be recognized by their color in ashed sections, were not observed. Degenerated cells, poor in material with staining affinity, were also poor in ash, and the large vacuoles characteristic of these cells in the usual preparations were seen in the corresponding incinerated cells.

The appearance of the erythrocytes (accompanying figure) was characteristic. The ash was concentrated at the peripheral border. Presumably this was an artefact caused by the fixation and drying of the specimen. However, the peripheral distribution of ash was as marked as that in the nuclei, and if one is an artefact of fixation, the question is properly raised whether the other is not also.

The total ash of a specimen from this case, incinerated in a crucible, was 2.7 per cent of the dry weight. This may be compared with the figure of 1.5 per cent of the moist weight, or approximately 6 per cent of the dry weight, commonly given for the normal spleen (Long: Textbook of Physiological Chemistry, ed. 2, Philadelphia, P. Blakiston's Son & Co., 1909, p. 14). The incineration study furnishes the explanation for this decrease in ash per unit of weight. The ash is concentrated in the nuclei, and nuclei are present in much larger numbers per unit of volume or of weight in the normal spleen than in the spleen in Gaucher's disease, the bulk of which is largely due to the cytoplasm of Gaucher's cells, or cerebroside cells, which is relatively poor in mineral matter.

INFLUENCE OF RETICULO-ENDOTHELIAL "BLOCKADE" AND SPLENECTOMY ON EXPERIMENTAL TRYPANOSOMIASIS AND SYPHILIS AND THE CHEMOTHERAPEUTIC PROPERTIES OF ARSPHENAMINE AND NEOARSPHENAMINE. JOHN A. KOLMER and JAY F. SCHAMBERG.

1. Partial blockade of the cells of the reticulo-endothelial system of rats by intravenous injections of india ink slightly increased the resistance to infection with Trypanosoma equiperdum.

2. This partial blockade, however, had no demonstrable effects on the trypanocidal activity of arsphenamine and neoarsphenamine.

3. Partial blockade in rabbits by intravenous injections of india ink had no appreciable effects on infection with Spirochaeta pallida.

4. The partial blockade likewise had no demonstrable effect on the spirocheticidal properties of arsphenamine and neoarsphenamine.

5. Removal of the spleens of rats had no appreciable effects on the development and course of infection with T. equiperdum injected intraperitoneally from five to seven days later.

6. Splenectomy, however, definitely reduced the trypanocidal activity of both neoarsphenamine and arsphenamine administered from five to seven days later, since the minimal curative doses were almost twice as large as those used for control animals.

7. Removal of the spleens of rabbits had no appreciable influence on the development and course of acute testicular syphilis following inoculation with S. pallida approximately from three to four weeks after operation.

8. Splenectomy, however, definitely increased rather than decreased the spirocheticidal activity of arsphenamine.

9. While partial blockade of the reticulo-endothelial system with india ink has no appreciable effects on the trypanocidal and spirocheticidal activity of arsphenamine and neoarsphenamine, it is apparent that splenectomy profoundly influences the chemotherapeutic activity of these compounds.

THE PHILADELPHIA INSTITUTE FOR MEDICAL RESEARCH AND ITS RELATION TO THE INTEREST OF PATHOLOGY IN PHILADELPHIA. L. G. ROWNTREE.

Dr. Rowntree outlined the purposes of the Philadelphia Institute for Medical Research and discussed investigations that are being undertaken by this group.

Book Reviews

Poliomyelitis. A survey made possible by a grant from the International Committee for the Study of Infantile Paralysis, organized by Jeremiah Milbank. Pp. 562, with 30 figures and 82 tables. Baltimore: Williams & Wilkins Company, 1932.

Dr. William H. Park, chairman of the International Committee for the Study of Infantile Paralysis, prefaces this volume with an acknowledgment of the contributions amounting to $280,000 made by Mr. Jeremiah Milbank for the support of investigations on poliomyelitis since 1928, and with a brief account of the composition and program of the Committee. This book is one of the results of the Committee's activities.

The volume is a critical bibliographic survey of all the available published articles on poliomyelitis. Approximately 8,000 references were consulted, and many of the most important papers were abstracted in considerable detail. The arrangement of the material for orderly presentation was made by a group working under the leadership of Dr. Helen Harrington. The book contains seven chapters, the titles and authorship of which are as follows: I. "Historical Summary," by Elizabeth F. Hutchin; II. "Etiology," by Helen Harrington; III. "Resistance and Immunity," by Helen Harrington; IV. "Symptomatology," by Josephine B. Neal; V. "Treatment," by Josephine B. Neal; VI. "Pathology," by Helen Harrington; VII. "Epidemiology," by Mildred Weeks Wells. Each chapter was read by one or more members of the International Committee. A topical analysis of the chapters and a detailed index greatly aid the reader in gaining access to the large amount of information recorded in the book.

Although the material is presented in the form of a survey and review of writings on poliomyelitis, the author of each chapter has introduced paragraphs of critical comment at the beginning or end of each important subdivision. These may be regarded both as opinions of the authors and as a consensus of the members of the Committee. As these conclusions are not summarized in any special section, the reader discovers them only after perusal of the text.

It seems unnecessary to present an analytic review of this large volume, which is itself a review of the voluminous literature on poliomyelitis. A description of the plan and contents of the book is sufficient to indicate to those interested in this disease that a compact assemblage of a vast amount of information has been provided for their aid. The work was done with such care and thoroughness that no important papers have been overlooked. All points of view have been presented by the authors with fairness and in objective detail. In these days of multiplicity of scattered publication, this documented epitome of knowledge of all aspects of poliomyelitis is a most serviceable guide and reference book.

The illustrations are excellent and interesting. The graphs and tabulations are succinct presentations of valuable statistical and epidemiologic material. The press-work is evidence of the skill and care of the publisher.

Books Received

INTRACRANIAL TUMORS. Percival Bailey, Professor of Surgery, University of Chicago. Price, $6.00. Pp. 475, with 155 figures. Springfield, Ill., Charles C. Thomas, Publisher, 1933.

PRACTICAL HEMATOLOGICAL DIAGNOSIS. O. H. Perry Pepper, M.D., Professor of Clinical Medicine, University of Pennsylvania; Assistant Chief of the Medical Clinic, Hospital of the University of Pennsylvania; and David L. Farley, M.D., Physician to the Pennsylvania Hospital, Philadelphia, and to the Cooper Hospital, Camden, N. J.; Associate in Medicine of the University of Pennsylvania. Price, $6.00. Pp. 562, with 3 colored plates. Philadelphia: W. B. Saunders Company, 1933.

ARBEITEN AUS DEM PATHOLOGISCHEN INSTITUT DER UNIVERSITÄT HELSINGFORS (FINLAND). Begründet von weil. Prof. Dr. E. A. Homén. Herausgegeben von Prof. Dr. Axel Wallgren. Neue Folge. Sechster Band, Drittes und Viertes Heft. Mit 69 Abbildungen im Text. Jena: Gustav Fischer, 1931.

SURGICAL PATHOLOGY. William Boyd, M.D., M.R.C.P.Ed., F.R.C.P., London, Dipl. Psych., F.R.S.C., Professor of Pathology, University of Manitoba; Pathologist to the Winnipeg General Hospital, Winnipeg, Canada. Third edition. Pp. 866, with 477 illustrations and 13 colored plates. Price, cloth, $10, net. Philadelphia: W. B. Saunders Company, 1933.

COLLECTED REPRINTS FROM THE LABORATORIES OF THE MOUNT SINAI HOSPITAL, NEW YORK, Louis Gross, M.D., Director, 1932.